Handbook of Medical Emergencies

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FORWARD

I wish to congratulate the authors for the splendid effort in compiling this Handbook of Medical Emergencies. The topics covered in this handbook are Very comprehensive. This handbook will be an invaluable reference book for Doctors working in emergency unit and wards of hospitals and in health clinics And polyclinics. With the availability of this handbook, it is hoped that the Quality of patient care in hospitals, health clinics and polyclinics will be Further enhanced.

Thank you.

Dr. Yao Sik Chi,
State Director of Health,
Sarawak

19th October, 1999

PREFACE

The idea of writing a little handbook on guidelines on the treatment of medical emergencies came while I was working as a medical officer in a small district hospital where I was expected to be an 'all rounder'. The spectrum of cases encountered in the district hospital (or in any hospital for that matter) is rather diverse and it would be such an invaluable help to have a reliable and yet simple handbook to refer to.

I started collecting useful management guidelines and information during my tenure at the district hospital, and began to compile these into a little handbook. Over the years, I have revised it 3 times (the last time being before this publication together with my colleagues) and have given several copies to junior doctors to use to assess the usefulness and relevance of the information therein. The feedback from them was rather encouraging. I then decided to make this handbook into a management guide for the Department of Medicine, Sarawak General Hospital as well as all other hospitals in Sarawak (with the blessing from the head of the Department of Medicine, Sarawak General Hospital and the state director of health of Sarawak). Dr Chew Peng Hong (head of the Department of Medicine) has helped me tremendously to restructure and edit this handbook. I would like to sincerely thank him for this.

This handbook is essentially a management guide for the use of junior staff like the house officers and medical officers during busy medical calls. Trainees in the field of internal medicine may also find this handbook useful. This handbook aims to provide users with more practical information rather than theoretical knowledge. As such, little attention is paid to the clinical features or the pathological basis of diseases. The stress here is on management, for example, the approach to a clinical condition, the drugs to give for treatment, the type of monitoring accorded, subsequent approach should tne initial treatment fail, etc. It includes not only the common emergency medical conditions but also many not-so-common conditions that can be potentially life-threatening.

This handbook was done by extensive research reading of numerous textbooks, reference books, subspecialty books, journals and review articles as I progressed through my brief medical career from a medical officer to a medical registrar and later, a general physician. Information was also obtained and verified from colleagues, some of whom were eminent figures in certain subspecialties. Opinions as well as criticisms were also gathered from the junior staff to make sure that, as end-users, they could make use of this handbook to the fullest.

It is our sincere and fervent wish as the authors, that our efforts have not resulted in just another handbook of medical emergencies to be displayed on the shelf in the medical library, but a book that is informative, handy and above all, helpful, in the management of various medical emergencies in the hospital. We

hope that all house officers as well as medical officers would find this book an asset during the course of their duties.

Dr Soo Hua Huat

9.9.99

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We would also like to thank representatives from Servier Malaysia, particularly Mr Sim Chi Tie, Ms Geraldine Chai and Ms Carol Sim, for helping and sponsoring the printing of this handbook.

ABBREVIATIONS

ABG	Arterial blood gas
ACE	Angiotensin converting enzyme
ADH	Antidiuretic hormone
AFB	Acid-fast bacillus
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ANA	Antinuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
aPTT	Partial thromboplastin time
AST	Aspartate transaminase
AV	atrioventricular
bd	bis die (twice a day)
BP	Blood pressure
BUSE	Blood urea and electrolytes
BW	Body weight
CEA	Carcinoembryonic antigen
cm	Centimeter
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airways pressure
CPK/CK	Creatininephosphokinase
CPR	Cardio-pulmonary resuscitation
Creat	Creatinine
CSF	Cerebrospinal fluid
CT	Computed tomography
CVP	Central venous pressure
CXR	Chest x-ray
D5%	Dextrose 5% solution
DIVC	Disseminated intravascular coagulation
DKA	Diabetes ketoacidosis
dl	Deciliter
DS	Dextrose saline
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiography
EEG	Electroencephalogram
EMG	Electromyography
ESR	Erythrocyte sedimentation rate
FBC	Full blood counts
FEV1	Forced expiratory volume in 1 second
FIO2	Inspired fraction of oxygen
FVC	Forced vital capacity
g	Gram
G6PD	Glucose 6-phosphate dehydrogenase

GXM	Group and crossmatch
HAV	Hepatitis A virus
Hb	Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
hr	Hour
HSV	Herpes simplex virus
ICP	Intracranial pressure
Ig	Immunoglobulin
IM	Intramuscular
INR	International normalized ratio
IPPV	Intermittent positive pressure ventilation
IV	Intravenous
JVP	Jugular venous pressure
kg	Kilogram
l	Liter
LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LP	Lumbar puncture
m	Meter
mcg	Microgram
mg	Milligram
min	Minute
ml	Milliliter
mm	Millimeter
mmH2O	Millimeter of water
mmHg	Millimeter of mercury
mmol	Millimole
MRI	Magnetic resonance imaging
NG	Nasogastric
nmol	Nanomole
NS	0.9% Normal saline
NSAID	Nonsteroidal anti-inflammatory drug
OD	omni die (once daily)
PaCO2	Partial pressure of carbon diaoxide
PaO2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PCWP	Pulmonary capillary wedge pressure
PEEP	Positive end-expiratory pressure
PEFR	Peak expiratory flow rate
PO	By month
PRN	pro re nata (as required)
PSA	Prostate-specific antigen
PT	Prothrom time
PTH	Parathyroid hormone

qid	quater in die (4 times a day)
RBBB	Right bundle branch block
SA	Sinoatrial
SC	Subcutaneous
SL	Sublingual
T3	serum triiodothyronine
T4	Thyroxine
tds	ter die sumendus (to be taken 3 times a day)
ug	Microgram
ul	Microliter
VDRL	Venereal diseases research laboratory
WBC	White blood cell
wk	week

CONTENTS

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7. Haematology

Dr Soo Hua Huat, Dr Lau Lee Gong

8. Poisoning

Dr Soo Hua Huat

9. Miscellaneous

Dr Soo Hua Huat, Dr Chew Peng Hong

10 Reference Intervals

11. Index

1. CARDIOLOGY

_ UNSTABLE ANGINA

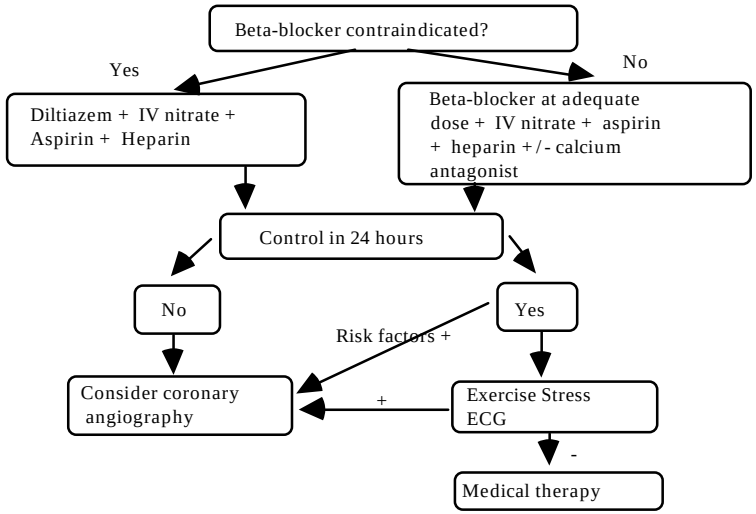
- The development of unstable symptoms carries a 10-20% risk of progression to acute MI.
- When ECG evidence of transient myocardial ishcaemia (ST-segment changes and /or T-wave inversions during episodes of chest pain) is present, it is almost always associated with critical stenoses in one or more major epicardial coronary arteries.

A. Definition

- ***The following groups of patient may be said to have unstable angina pectoris:***
  1. Patients with new onset (<2months) angina that is severe and/or frequent (>3episodes/day);
  2. Patients with accelerating angina, ie. those with chronic stable angina who develop angina that is distinctly more frequent, severe, prolonged, or precipitated by less exertion than previously;
  3. Those with angina at rest.

B. Management

Algorithm for the management of unstable angina



1. General measures:

1.1

- Patient should be admitted to CCU for observation. The cardiac rhythm should be monitored for 24-48 hours. The patient is encouraged to report any recurrence of pain.
- Bed rest, sedation and analgesics should be administered as in acute myocardial infarction.
- Blood pressure should be taken every 15-30 mins for a few hours and then every 1-2 hours.
- IV line for drug administration should be established.
- Oxygen should be given via a nasal prong.
- ECG and cardiac enzymes should be serially monitored to detect AMI. Other risk factors for coronary artery disease (such as diabetes mellitus, hypercholesterolaemia) as well as precipitating factors (such as anaemia) should be looked for and treated if present. CXR should also be taken.

2 Treatment of Ischaemia:

- Usually, beta-blockers, nitrates, and calcium antagonists are used in combination.

a. Beta-blockers:

- Reduce myocardial oxygen demand by inhibiting the increases in heart rate and myocardial contractility caused by adrenergic activity.
- If not contraindicated, give ***propranolol*** 20-40 mg every 8 hours or ***metoprolol*** 50mg every 12 hours and titrate quickly to achieve adequate doses (target HR of 55-60 bpm), usually metoprolol 100mg bd or equivalent dose of another beta blocker.
- Withhold dose if systolic blood pressure is <100mg Hg or if pulse is <50 / min.
- They are contraindicated in severe heart failure, history of bronchospasm, atrioventricular nodal block, severe peripheral vascular disease, and marked resting bradycardia (HR <50-55 bpm).

b. Nitrates:

- First- line agents for treatment of angina.
- ***Sublingual nitroglycerin*** 0.3-0.5mg (tablets available as 0.3mg, 0.4mg or 0.5mg) can be given for rapid relief of pain and repeated at 5-min intervals to a maximum of 3 tabs. Peak action occurs within 2 min and continues for 15-30mins .
- In general, ***IV nitroglycerin*** is preferred to oral or transdermal preparations. IV dosing should be considered in patients who are unresponsive to initial sublingual therapy.
- IV nitroglycerin (50mg in 250ml of NS or D5% = 200mcg / ml; 10mcg / min = 3ml / hr) should be commenced at 5-10 mcg / min and increased by 5-10 mcg / min every 5-10 mins, up to 100-200mcg / min. Titrate to eliminate all episodes of chest pain and do not lower the systolic blood pressure >10 - 15% or to < 100mmHg.
- After the patient has been pain free for about 24 hours, oral or transdermal nitrates can be started, and IV infusion should then be tailed off.

Transdermal nitrates dosing can also be given to patients who respond well to initial oral therapy.

- **Preparation** **Dose**

Isosorbide dinitrate	5-40mg tds
2% nitroglycerin ointment	0.5 - 2.0 in. 4-6hrly
Sustained-release GTN patches	5-15mg OD
Isosorbide mononitrates	20-120 mg daily in divided doses

c. Calcium channel blockers:

- These agents are not recommended as first or second line but as third line agents. They are added if the blood pressure allows this addition to be safely made. If used, nondihydrophyridines group eg. ***diltiazem*** or ***verapamil*** is preferred.
- Calcium channel blockers do not decrease mortality in patients with unstable angina.
- They cause a variable degree of coronary and peripheral artery vasodilation and have negative inotropic effects. They decrease cardiac afterload hence, preserve or increase cardiac output despite the negative inotropic effects.
- Short-acting dihydrophyridine calcium antagonists eg. ***nifedipine*** should be avoided as they tend to cause reflex tachycardia unless they can be used in combination with beta-adrenergic blockers.
- Verapamil or diltiazem should not be given if sinus node disease, bradycardia, AV block, heart failure, or left ventricular dysfunction is present. Verapamil is contraindicated in acute infarction.
- Doses of selected calcium channel antagonists:

Verapamil	40-120 mg tds
Diltiazem	30-90 mg tds
Nifedipine R	20-40mg bd
Amlodipine	2.5-10 mg od
Felodipine	5-10 mg od to bd

3. Antiplatelet agents.

- ***Aspirin*** 300mg chewed and swallowed for a rapid effect and then 150mg daily. Aspirin (given concomitantly with anticoagulants) has been proven effective in clinical trials to prevent fatal and nonfatal infarction in patients with unstable angina.
- ***Ticlopidine*** 250mg bd may be useful in patients with aspirin hypersensitivity or intolerance.

4. Anticoagulants:

- Intravenous ***unfractionated heparin*** appears to decrease the incidence of MI in patients with unstable angina. It should be given as a bolus dose of 5000 U followed by an infusion of 1000 U per hour. The infusion dose is adjusted by regular monitoring of aPTT, keeping it between 1.5 to 2.5X control. This should be maintained for 2-5 days.

- ***Low molecular weight heparin*** (LMWH) has been shown in a few trials to be as good if not better than unfractionated heparin in reducing cardiovasular events as well as overall mortality.
- LMWH available includes dalteparin, nadroparin, enoxaparin, etc.

5. Correction of precipitating conditions such as hypertension, anaemia, infection, or hypoxaemia.

6. Invasive therapy:
- ***Urgent cardiac catheterization*** should be considered for the patient with ***(i) chest pain with objective evidence of ischaemia that persists for more than 24-48 hours after aggressive medical therapy (ii) recurrrent ischaemic episodes despite optimal medical therapy, and (iii) hypotension or severe heart failure during medical therapy.*** Do not refer patients who would not accept further intervention (PTCA or CABG).
- ***Elective cardiac catheterization*** should be considered for the patient with unstable angina and any of the following risk factors:
  Prior angioplasty or bypass surgery, congestive heart failure or depressed left ventricular function, life-threatening ventricular arrhythmias, recurrent low threshold ischaemia, ECG changes during pain or a noninvasive exercise or pharmacological stress test indicating a high likelihood of severe coronary artery disease.

7. If the patient`s symptoms are controlled promptly by initial therapy (with no indications for cardiac catheterization as mentioned above) and remains pain-free for 48-72 hours, an exercise ECG should be obtained near the time of hospital discharge to risk-stratefy the patients; he should then be managed accordingly.

_ ACUTE MYOCARDIAL INFARCTION

A. Risk factors

- Abnormal serum lipids (elevated total cholesterol, high LDL cholesterol, low HDL cholesterol), smoking, hypertension, family history, age, male sex, diabetes mellitus.

B Anatomical Correlations

Vessels occluded	Areas of Infarction

Anterior descending artery	Anterior wall of the left ventricle (LV), anterior part of the septum (affect intraventricular conduction)
Circumflex artery	Lateral or inferior walls of the LV & posterior wall of LV
Right coronary artery	Posterior and inferior surface of the LV, posterior part of septum, right ventricle (RV). A-V node in 90% & SA node in 60% of cases (thus inferior and posterior infaction may be associated with A-V conduction disturbances)

C. Clinical Features

- Pain - characteristically retrosternal, > 20 minutes, radiation to the arms, neck or jaw. Severe and crushing in nature, not relieved by rest or GTN. May be epigastric, radiating to the back.
- Symptoms frequently associated with sweating, nausea, vomiting, dyspnoea, weakness, apprehension, restlessness and anxiety.
- Rarely painless, masquarading as acute left ventricular failure, syncope, CVA or unexplained shock
- 25% are asymptomatic and detected on routine ECG.
- Non-specific physical signs - pallor, sweating, irregular pulse, hypotension, and 4th heart sound may be present.

D. Investigations

1. Electrocardiogram (ECG):

- ECG provides valuable information on the size, extent, age of the MI and some anatomical correlations of vessels occluded.

a. Q wave infarction:

ECG changes	**Onset**	**Duration**
ST elevation	within minutes or hours	days or weeks
T inversion	immediate or hours	several months
Q wave	hours or days	remain indefinitely

(Q wave - _1mm wide[0.04s] and/or _2mm deep [0.2mV] or >25% of the amplitude of the R wave)

b. Non-Q wave infarction:

- Changes are prolonged ST depression and T inversion.

- Non-Q wave infarction generally results from incomplete occlusion or spontaneous lysis of the thrombus and it is associated with a higher incidence of reinfarction and recurrent ischaemia.

- Localization of infarction area:

Infarct site	**Leads showing main changes**
Anterior	
Small	V3-V4
Extensive	V2-V5
Anteroseptal	V1-V3
Anterolateral	V4-V6, I, AVL
Lateral	I, II, AVL
Inferior	II, III, AVF
Posterior	V1, V2 (reciprocal)
Subendocardial (non-Q)	Any lead

2. Cardiac enzymes:

- Necrotic cardiac tissue releases cellular enzymes:

Enzyme	**Earliest Rise, h**	**Peak, h**	**Norma-lize, days**	**Non-cardiac sources of Enzyme**
CK-MB	3-6	12-24	1-2	
CK	6-8	24-30	3-4	Intramuscular injections, defibrillation, convulsions, vigorous exertion, cerebral infarction, etc
AST	8-12	36-48	3-5	Alcoholism, hepatitis, biliary obstruction, cardiac arrest
LDH	12-24	48-96	7-10	Haemolytic anaemia, pulmonary infarction, neoplastic disease.
HBD	12	72	10-14	

CK - creatine kinase
AST - aspartate aminotransferase
LDH - lactic dehydrogenase
HBD - hydroxybutyrate dehydrogenase *(a measure of LDH1 and LDH2 concentration can be obtained by measuring serum HBD activity)*

- ***Enzymes*** are usually estimated for the first 3 days following a suspected myocardial infarction.
- ***Troponin T:***
  * A cardiac specific protein (a cardiac muscle specific protein that binds the troponin complex to the tropomysin strain and neighbouring tropomysin molecules).

* It is not detectable in healthy individuals.
* Troponin T appaers in the circulation as early as 2.5 hours after onset of chest pain (cf. 3 hours for CK-MB) and remains elevated for more than 7 days post-infarction.
* Can be measured using a rapid kit.

3. Other diagnostic techniques:

a. Radionuclide studies:

- ***Pyrophosphate scan*** – useful when the ECG is unhelpful due to preexisting abnormalities (eg. LBBB) or when patient presents late and cardiac enzymes are no longer elevated or are unreliable (limitations: test is only optimal 2-7 days after AMI, insensitive for small infarction). However, this test is only available in specialised centres.

b. Echocardiography – images the cardiac structures, pericardium and aorta, allowing identification of regional wall motion abnormalities, valvular abnormalities as well as global, left and right ventricular function.

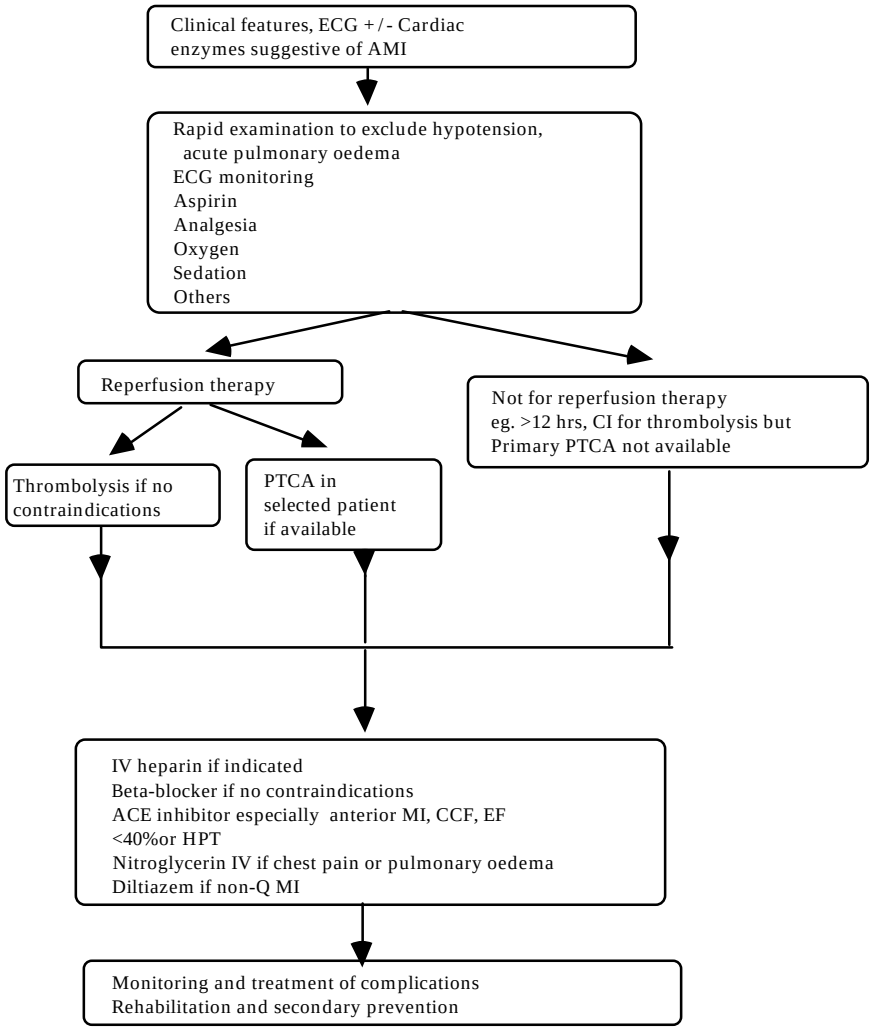
c. Coronary angiography is performed where interventional treatment is indicated. In the peri-infarction period, thrombus is known to appear and vanish, with reperfusion spontaneously.

4. General investigations:

- FBC, BUSE, blood sugar, cholesterol (within 24 hrs or after 3 mons of MI), portable CXR, se creat.

E. Management of Acute MI

 # Algorithm for the treatment of AMI:



I General Management

1. ***Bed rest*** for 2-3 days in uncomplicated cases.
2. ***ECG monitoring*** for at least 48 hours.
3. ***Oxygen*** at 2-4L/min for 2-3 hours & continues thereafter if SaO2 remains (<90%) or if there is shortness of breath or tachypnoea.
4. A tablet of ***aspirin*** 300 mg should be given to the patient to chew immediately.
5. ***Analgesia:***

- ***Sublingual nitroglycerin (***0.3-0.5mg) - should be given to patient in the absence of hypotension repeated every 5 minutes till 3-4 doses have been given.
- ***Morphine*** 5-10mg IV slow bolus with antiemetic.
- Patients who have recurrence of symptoms after given SL GTN and morphine should be started on ***IV GTN.***

5. ***Regular leg exercises*** and ***low dose heparin*** (eg. subcutaneous 5,000 units bd) to prevent deep vein thrombosis.
6. ***Sedation*** with small oral doses of diazepam or lorazepam.
7. ***Diet and bowel care*** - for the first day after MI, diet should be liquid or soft, stool softeners or mild laxatives are routinely given.
8. ***Potassium levels*** should be maintained at 4-5 mmol/l.

II Specific management to reduce infart size and to improve mortality

1. Thrombolytic therapy:

- Administration of fibrinolytic agents can achieve early reperfusion in 50-70% of patients (compared with a spontaneous reperfusion rate of < 30%) and has been shown to reduce the extent of ventricular damage, and mortality rates associated with myocardial infarction.

_ **All patients fulfilling the following criteria without contraindication should be given thrombolytic therapy.**

a. Clinical:

- Chest pain or chest-pain-equivalent syndrome consistent with acute myocardial infarction _ 12 hours from symptom onset with:

b. ECG (either one):

- _ 1 mm ST elevation in _ 2 contiguous limb leads.
- _ 2 mm ST elevation in _ 2 contiguous precordial leads.
- New left bundle branch block.
- True posterior MI (Tall R wave in V1 with ST depression; exclude other causes of tall R wave [eg. RBBB, RVH, WPW syndrome]; right ventricular infarction[ST elevation V4R]).

 # Cardiogenic shock: emergency catheterization and revascularization if possible; consider thrombolysis if catheterization not immediately available.

 # Age is not a limiting factor - can be given up to 80 yo or older if benefit-to-risk ratio seems favourable.

 # Should be avoided in patient with ST segment depression without concomitant ST segment elevation or with normal ECG.

- **Contra-indications**:
  - ***a. Absolute contraindication:***
    - Altered consciousness.
    - Active internal bleeding.
    - Prolonged or traumatic CPR (>10 min).
    - Known spinal cord or cerebral arteriovenous malformation or tumour.
    - Recent head trauma.
    - Known previous haemorrhagic cerebrovascular accident or stroke within 6 months.
    - Intracranial or intraspinal surgery within 2 months.
    - Trauma or surgery within 2 weeks, which could result in bleeding in a closed space.
    - Persistent blood pressure > 200/120 mmHg.
    - Known bleeding disorder.
    - Pregnancy.
    - Suspected aortic dissection.
    - Previous allergic reaction to Streptokinase or APSAC (or prior use within 1 yr) - should use tPA.
  - ***b. Relative contraindications:***
    - Chronic uncontrolled hypertension (diastolic BP >100mmHg), treated or untreated.
    - Any haemorrhagic retinopathy.
    - Ischaemic or embolic CVAs in the past.
    - Major trauma or surgery, >2 weeks and < 2months previously.
    - Oral anticoagulation, therapeutic.
    - Active peptic ulcer disease, or haeme-positive stools.
    - Acute pericarditis, infective endocarditis, intracardiac thrombus.
    - Subclavian or internal jugular cannulation.

- **Thrombolytic agent**:
  - ***a. Streptokinase:***
    - Cheap, effective and relatively safe.
    - Antigenic, and its repeated use in a period from 5-7 days to 1 year after first exposure is not recommended.
    - Invasive vascular procedures should be delayed for 24 hours after streptokinase.
    - ***Dosage*** - 1.5 million units in 100ml saline infused over 60 min.
    - May premedicate with hydrocortisone 100mg IV and diphenhydramine 25-50mg IV.
  - ***b. Recombinant tissue plasminogen activator (rtPA/Alteplase):***
    - Relatively expensive.
    - Non-antigenic, and is the agent of choice if a second or subsequent attempt at thrombolysis is necessary.
    - Short acting, invasive procedures can be performed within 20-30 min of stopping infusion.

- ***Dosage*** - (i) For adults who weigh >65kg - 15mg bolus followed by 50mg over 30 mins and then 35mg over 60 mins. (ii) For adults who weigh <65kg - 15mg bolus followed by 0.75mg / kg over 30 mins (not to exceed 50mg) and then 0.5mg / kg (up to 35mg) over next 60 mins.
- Reconstitue 100mg with saline or D5W to 100ml.
- Heparin iv bolus followed by infusion to keep PTT at 2X control value should be given for 48-72 hr when rtPA is completed (not necessary with other thrombolytic therapy).

c. Anisoylated plasminogen striptokinase activator complex (APSAC/Anistreplase):

- Single bolus injection dose, and has principally been used for out-of-hospital thrombolysis.
- It cross-reacts antigenically with streptokinase.
- May premedicate as for streptokinase.
- ***Dosage*** - 30 units as slow intravenous injection over 2-5 min.

Choice of thrombolytic agents:

- ***Streptokinase*** remains the thrombolytic therapy of choice.
- ***rtPA*** - limits to patient < 40 yrs, large anterior MI, treatment within 4 hrs, patient who have had streptokinase or APSAC in the past year or BP < 100mmHg systolic.

Monitoring

- Fibrinogen level and PTT should be monitored 6 hours after the infusion.
- Reperfusion is recognized clinically by the cessation or reduction of pain, resolution of ST elevation or rapid evolution of ECG to Q waves, reperfusion arrhythmias (commonly AVIR) and an early peak of CK (by 12 hours).

Complications of thrombolytic therapy:

a. Hypotension during streptokinase infusion:

- Usually reversed by slowing the infusion.

b. Allergic reaction to streptokinase:

- Give chlorpheniramine 10mg IV and hydrocortisone 200mg IV. May need to stop SK if severe.

c. Uncontrollable bleeding:

- Stop the infusion.
- Fresh frozen plasma and cryoprecipitate can be given to reverse the lytic state.
- As a last resort, give tranexamic acid 1g (10mg / kg) IV over 10 min.

d. Reperfusion arrhythmias:

- Most commonly runs of accelerated idioventricular rhythm (AIVR).
- AIVR is usually transient & asymptomatc and does not require therapy. When AIVR is associated with haemodynamic deterioration or it precipitates VT or VF, administration of atropine, isoprenaline or overdrive atrial pacing is effective treatment.

e. Invasive vascular procedures needed:

- If venepuncture is necessary, use a 22 gauge needle and compress the puncture site for 10 min.
- CV lines should be inserted via an antecubital fossa vein (percutaneously or by cut-down).
- If temporary pacing is required within 24 hours of thrombolytic therapy, the wire should ideally be placed via an antecubital fossa vein. If there is no suitable superficial vein, the options are a cut-down or placement via the femoral vein.

2. Antiplatelet agents:

- ***Aspirin*** has a beneficial effect by significantly reducing mortality. Aspirin therapy enhances the benefit of thrombolysis and should be given irrespective of the thrombolytic agent used
- Low dose aspirin 75-150mg / day should be prescribed for all patients with MI to prevent coronary rethrombosis (A first dose of 300 mg should be given as soon as possible at the A&E as mentioned above).
- If possible, the aspirin should be chewed and then swallowed for maximal therapeutic benefit.

3. Beta-Blockers:

- IV Beta-blockers given immediately and / or long term beta-blockers have been shown to reduce mortality from MI and improve survival.
- Therefore, intravenous beta-blockers are indicated in most patients with acute MI who present within the first 4-6 hours after the onset of symptoms, eg. ***propranolol*** (0.1mg / kg IV divided into 3 doses every 5-10min, followed in 1 hour by 20-40 mg oral dose every 6-8 hr) or ***atenolol*** 5-10mg IV, followed by 100mg / day orally or IV metoprolol 5mg repeated at 5 min intervals to a dose of 15mg followed by 6hrs later by 50mg bd.
- If IV beta-blockers are not available, oral beta-blockers should be given to all patients before they leave coronary care unit provided they have no obvious contraindications.
- They are contraindicated in severe heart failure, history of bronchospasm, atrioventricular nodal block, severe peripheral vascular disease, and marked resting bradycardia (HR <50-55 bpm).

4. Nitroglycerin:

- May have a beneficial effect on infarct size but no independent effect on mortality reduction in AMI.
- ***Intravenous nitroglycerin*** is initiated as a 5-10mcg / min infusion (50mg in 250ml of NS or D5% = 200mcg / ml; 10mcg / min = 3ml / hr) that is increased in 5-10mcg / min increments at 10-15 min intervals. Blood pressure should be closely monitored and the dose should not be increased further once there has been a 10-15% reduction in systolic BP or if SBP <100 mmHg.

5. Angiotensin converting enzyme (ACE) inhibitors:

- ACE inhibitors improve mortality from AMI. They should be given as soon as the clinical state allows, but should be given orally, not intravenously.

- Benefits are greatest in those patients most prone to infarct expansion and remodelling (eg. large MI, anterior MI, clinical LV dysfunction, and hypertension). In this group of patients, treatment should be continued indefinitely.
- In unselected group of patients (eg. inferior MI, non-Q wave MI), treatment can be stopped after 4-6 weeks in patients who are subsequently shown, by objective measure of LV function, not to have significant LV dysfunction.
- Recommended starting dose and target doses:

ACE inhibitor	Starting dose	Target dose
Enalapril	2.5mg	10mg bd
Captopirl	6.25mg	50mg tds
Perindopril	2mg	4mg od

6. Calcium channel blockers:

- The role of calcium channel blockers in AMI is limited. Routine use is not recommended.
- Calcium channel blockers are indicated for unstable or postinfarction angina and persistent chest pain when no relief from nitrates is apparent. (Generally, the rate-limiting calcium channel blockers such as verapamil and diltiazem are more useful than the dihydropyridines)
- ***Diltiazem*** may be beneficial in patients with non-Q-wave infarction.

7. Prophylatic Antiarrhythmias:

- Currently there is no evidence that the use of ***prophylactic antiarrhythmics*** confers any benefit and may be harmful.
- However, recent data suggest that ***amiodarone*** (200 mg daily over 2 years) may reduce arrhythmic death in patients with non-sustained ventricular arrhythmias (ventricular tachycardia or frequent premature depolarization) and impaired LV function (EF<40%).

8. Anticoagulants:

- Heparin, 5000units IV bolus, followed by a 1000U / hr continuous infusion titrated to maintain PTT at 2X control value may be indicated in ***(i) LV aneurysm (ii) atrial fibrillation (iii) poor ejection fraction (iv) large or anterior MI.(v) post-infarction angina and (vi) rt-PA therapy/***
- The target aPTT should be 1.5 to 2.5X normal. It is often a prelude to long term anticoagulation using oral warfarin except in (v) & (vi) above when only short term heparinization is required without the need for oral warfarin.

9 Primary coronary angioplasty:

- If available, should be considered, particularly for patients:
  a. With contraindications to thrombolytic therapy.
  b. Presenting within 4 h of a large anterior MI.
  c. In whom MI may be due to a vein graft occlusion.
  d. With cardiogenic shock.

III. Complications of MI.

- In the acute phase (the first 3 days), cardiac arrhythmias, cardiac failure and pericarditis are the most common complications. Later, recurrent infarction, angina, thromboembolism, mitral regurgitation, and ventricular septal or free wall rupture may occur.

a. Cardiac arrhythmias:

- Common arrhythmias that may occur include ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation, atrial fibrillation, sinus bradycardia, sinus tachycardia, and various conduction disturbances (such as complete heart block, bundle branch block, etc).
- For the management of the various types of arrhythmias, please refer to the respective section.

b. Cardiac failure & cardiogenic shock:

- Heart failure after AMI is graded according to a clinical classification - the Killip`s classification as shown:

Killip classification of patients with acute myocardial infarction

Class	Definition	Approximate mortality
Class I	Absence of rales over the lung fields and absence of S3	8%
Class II	Rales over 50% or less of the lung fields or the presence of an S3	30%
Class III	Rales over more than 50% of the lung fields (frequently pulmonary oedema)	44%
Class IV	Shock	80-100 %

- For the management of heart failure and cardiogenic shock, please refer to the section on acute heart failure and cardiogenic shock.
- Severe heart failure may also follow ventricular septal rupture or mitral valve papillary muscle rupture. Both these conditions have grave prognosis and early surgical management should be instituted.
- Ventricular asynergy and papillary muscle dysfunction may produce mild mitral regurgitation in association with heart failure. In these cases no specific treatment is necessary for the mitral regurgitation.

c. Thromboembolism:

- Bed rest and cardiac failure contribute to the common occurrence of thrombosis and embolism associated with AMI.
- DVT is the commonest and pulmonary embolism may result from this.
- Early ambulation (if no contraindication) and prophylactic anticoagulation (subcutaneous unfractionated heparin 5000 to 10000 U bd or LMWH) help to reduce this complication.

d. Cardiac rupture:

- This results in almost immediate cardiac tamponade and is usually fatal within a few minutes.
- Electromechanical dissociation is the classical presentation and treatment is rarely successful.

e. Pericarditis:

- This is characterised by sharp chest pain and a pericardial rub.
- It frequently occurs in the first few days after an AMI especially following anterior wall infarction.
- Anticoagulation should be avoided in these patients and antiinflammatory medication is usually a successful treatment.

f. Postinfarction angina:

- This should be managed along the line of unstable angina (with beta-blockers, aspirin, nitrates, heparin +/- rate-limiting calcium antagonists), and a view to early interventional management should be kept in mind.

g. Left ventricular aneurysm:

- This is often a late complication of myocardial infarction. The patient presents with heart failure, arrhythmias or recurrent emboli.
- The diagnosis is confirmed by echocardiogram. Treatment includes antiarrhythmic drugs, anticoagulants and heart failure medications.
- Surgical removal of the aneurysm (aneurysmectomy) may be necessary.

h. Other complications:

- These include the shoulder-hand syndrome (pain and immobility of the left arms in the weeks and months following an AMI) and the postmyocardial infarction Dressler`s syndrome (a combination of pericarditis, fever and a pericardial effusion which occurs weeks to months after an AMI).

IV. Rehabilitation

- Generally, the length of hospitalization for uncomplicated cases is 7-10 days.
- Patients should initially be kept at ***bed rest.*** Within 24 hours after admission, patients with an uncomplicated course should begin sitting in a chair, may use a bedside commode, and should be encouraged to help themselves to shave, and eat (DVT prevention and fulfulling biological functions).
- Patients should be encouraged to ***begin walking*** in the room on the third day after admission and should be fully ambulatory by 5-7 days (Activities to ward off boredom).
- ***Work*** - patients in a sedentary occupation can usually return to works 4-8 weeks after discharge, those with more active jobs should return after 3 months.
- ***Driving*** - driving can be resumed after about 6-8 weeks.
- ***Exercise*** - regular aerobic exercise, preferably in a structured setting, is recommended for those patients who have had an uncomplicated course and are at low risk for subsequent of cardiac events.

V. Secondary prevention

1. Modification of risk factors is important eg. stop smoking, regular exercise, control of dyslipidaemia, hypertension, and DM

a. Smoking:

- Smoking is detrimental to the patient's condition after an AMI and can nullify the potential benefits of all forms of treatment.
- A systematic effort should be made to help the patient stop smoking.
- Oral or transcutaneous nicotine preparations can play a temporary adjunctive role but should not be used during the period just after the MI.

b. Dyslipidaemia:

- All patients should undergo assessment of serum lipid levels, and unfavorable levels should be treated intensively. Evaluation of serum lipid levels should be performed at the time of admission (within 24 hours) before significant AMI-related alterations occur or 3 months after the AMI.

- Treatment should be initiated during hospitalization for AMI after the patient's condition has stabilized.
- The desirable lipid levels are:
  LDL cholesterol <100mg/dl (2.6 mmol/L);
  HDL >35mg/dl (0.9 mmol/L).
- Diet control and exercise remain the mainstay of therapy.
  In many instances, pharmacological therapy with a statin or other appropriate lipid lowering agents will be indicated**.**

c. Hypertension:

- Adequate control of hypertension is essential after an AMI. Appropriate nondrug therapy (eg. sodium restriction, weight reduction, <2 drinks of alcohol daily, and exercise) is the initial approach that should be combined with pharmacological treatment to achieve optimal control of blood pressure (ie. a goal of <140/90mmHg).
- The agents of choice to start with for most patients after AMI are beta-blockers or ACEIs.

d. Exercise:

- Regular aerobic exercise should be prescribed for patients in stable condition at the frequency, intensity and duration indicated by testing and clinical judgement.
- The prescription is based on the effort tolerance, which should document absence of cardiac signs and symptoms at the prescribed exercise levels.

2. Medication:

a ***Beta-blockers:***

- In the absence of contraindication, beta blockers should be given as soon as possible and preferably indifinitely following MI.
- The drug can be started during the acute phase by IV or oral routes.
- Compensated congestive heart failure and asymptomatic LV dysfunction are not necessarily absolute contraindications to therapy with beta-blockers.
- Those with intrinsic sympathomimetic action should be avoided.

b ***Aspirin :***

- Aspirin is recommended for all patients with AMI (without CI) and should be continued indefinitely.
- Low dose aspirin 75-150mg od is effective.
- For those patients unable to tolerate aspirin, ticlopidine is an alternative antiplatelet agent (250mg bd).

c ***Warfarin***;

- Patient with large anterior MI should be considered for treatment initially with warfarin for 3-6 months, and later, can be treated with aspirin alone indefinitely.
- Patients with severe LV dysfunction, AF or left ventricular aneurysm should be treated with warfarin chronically to decrease the risk of systemic embolization.

d ***ACE Inhibitors:***

- In high-risk patients with recent MI (eg. large anterior MI, CHF, left ventricular aneurysm), therapy with ACE Inhibitors should be continued for at least 1-2 years and continued indefinitely in those with persistent left ventricular dysfunction (LVEF <40%).
- For low risk patient, ACE inhibitors can be continued for 4-6 weeks.

VI. Review of symptoms and Risk stratification after MI

1. Review of symptoms:

- Post-infarction angina is an important symptom and is usually considered to be an indication for coronary angiography in patients otherwise suitable for revascularization.
- Breathlessness is often a result of left ventricular failure.
- Palpitation usually requires 24-hour ambulatory minitoring. Ventricular extrasystoles and non-sustained VT do not usually require treatment.
- Sustained VT requires prompt investigation. Coronary angiography is necessary to exclude critical multivessel disease. Empirical treatment with either sotalol or amiodarone is reasonable.

2. Stress testing:

- Submaximal stress ECG can be performed 7-10 days after an uncomplicated MI, and patients with a positive test result should undergo angiography and revascularization if needed.
- Maximal stress exercise test can be safely done 4-6 weeks after MI.
- A siginificant proportion of recurrent events occur during the first few weeks after infarction and therefore early stress testing is preferred.

3. Radioisotope perfusion scanning (thallium 201) and stress echocardiography can also be used in patients who are unable to perform stress exercise. It has the additional advantage of being able to identify "stunned" or "hibernating" myocardium.

4. Coronary angiography may be needed in the following group of patients (immediate predischarge up to 8 weeks after discharge):

- Postinfarction angina pectoris.
- Patients with evidence of myocardial ischaemia on laboratory testing - see section on stress ECG below.
- Patients with the need to return to unusually active and vigorous physical employment #.
- Patient with a left ventricular ejection fraction <40%#.
- Otherwise uncomplicated and asymptomatic patients who are <45 #.
- Patients with uncomplicated non-Q-wave infarction without evidence of myocardial ischaemia on noninvasive laboratory testing #.

These indications are acceptable but may be controversial.

Exercise test parameters associated with poor prognosis and/or increased severity of coronary artery disease

1. ***Duration of symptom-limited exercise:***
- Failure of complete Stage II of Bruce protocol or equivalent work load (_6.5 METS) with other protocols.

2. ***Exercise heart rate at onset of limiting symptoms:***
- Failure to attain heart rate _120/min (off beta blockers).

3. ***Time of onset, magnitude, morphology and postexercise duration of abnormal horizontal or downsloping ST-segment depression.***
- Onset at heart rate <120/min or _6.5METS.
- Magnitude _2.0 mm.
- Postexercise duration _6 min.
- Depression in multiple leads.

4. ***Systolic blood pressure response during or following progressive exercise.***
- Sustained decrease of >10 mmHg or flat blood pressure response during progressive exercise.

5. ***Other potentially important determinants:***
- Exercise-induced ST-segment elevation in leads other than AVR.
- Angina pectoris during exercise.
- Exercise-induced U wave inversion.
- Exercise-induced ventricular tachycardia.

VII Right Ventricular Infarction

- About 1/3 of patients with inferoposterior AMI have associated RV infarct.
- Therefore, R-sided precordial leads should be done in patients with Inferoposterior Infarct to look for signs of RV infarction eg. ST elevation particularly in V3R, V4R.
- The clinical presentation is that of hypotension, high JVP with Kussmaul's sign, hepatomegaly, peripheral oedema, and clear lung.
- Correct diagnosis of RV pump dysfunction may require measurement of PCWP with Swan-Ganz catheter.
- The distinction between LV heart failure from RV heart failure is therapeutically important. Patients with RV infarction are dependent on an elevated RV filling pressure to maintain cardiac output, and it is important to avoid or prevent decreases by the use of diuretics or nitrates.
- Volume infusions may produce improvement in cardiac output, and hypotension should be treated initially with isotonic fluid boluses (up to 3 litres) to achieve a blood pressure of 90mmHg or a PCWP of 15-18mmHg. Clinical monitoring by listening for crackles at the lung bases should be frequently performed.
- Inotropic medications are required if IV fluid therapy achieves a PCWP of 15 mmHg with persistent hypotension.

_ HYPERTENSIVE CRISIS

1.19

Cardiology

- ***Hypertensive crisis*** is defined as a substantial acute increase in blood pressure, usually with diastolic blood pressure over 120 mmHg with or without end-organ damage.
- It can be further classified into:
  - ***(i) Hypertensive emergencies*** - increased blood pressure with evidence of end-organ damage or dysfunction.
    - End-organ manifestations include [1] retinal eg. papilloedema [2] cardiac eg. pulmonary oedema, myocardial ischaemia such as unstable angina or infarction [3] neurological eg. severe headache, mental status changes, seizure, coma and [4] renal eg. acute renal failure.
  - ***(ii) Hypertensive urgencies*** - elevation of blood pressure to a level which may be potentially harmful, but without signs, symptoms or other evidence of end-organ dysfunction.

A. Management

1. General principles:

- In ***hypertensive emergencies,*** blood pressure control should be accomplished within a few hours to reduce the risk of permanent damage or death (diastolic of 100-110 mmHg may be adequate for the first 24 hours). IV antihypertensive agents should be used.
- In ***hypertensive urgencies,*** blood pressure control can be accomplished more slowly with oral antihypertensive agents within 24-48 hrs to a diastolic level of 100-110 mmHg initially. Excessive or rapid decreases in BP should be avoided to minimize the risk of cerebral hypoperfusion or coronary insufficiency.
- BUSE, creatinine, urinalysis, CXR and ECG should be performed urgently.
- Drugs of choice for management:
  a. ***Coronary artery disease and heart failure:*** IV nitroprusside or nitroglycerin
  b. ***Pheochromocytoma***: IV phentolamine or alpha-blocker eg. prazosin
  c. ***Aortic dissection:*** IV beta-blockers or labetalol +/- nitroprusside
  d. ***Pulmonary oedema:*** IV frusemide, IV nitroprusside, ACE inhibitors
  e. ***Hypertension in pregnancy:*** Hydralazine, labetalol and magnesium sulphate
  f. ***Stroke:*** Beta-blockers, diuretics or ACE inhibitors.
- ***Sublingual nifedipine*** SHOULD BE AVOIDED.
- IV diazoxide should be discouraged.

2. Oral antihypertensive agents:

- Can be used in patients with hypertensive crisis when urgent but not immediate reduction of BP is indicated. ***Combination therapy*** is necessary for most cases when diastolic blood pressure is > 110 mmHg.
- ***Beta-blockers*** eg. atenolol 100mg ***with or without diuretics,*** or oral ***captopril*** 12.5mg ***with or without diuretics*** may be all that is required. If

nifedipine is contemplated, it should be used with careful monitoring of blood pressure to avoid precipitous drop.

3. Parenteral antihypertensive agents:

- Indicated in hypertensive emergencies or individuals with hypertensive urgencies who are in need of emergency surgery.

a. Sodium nitroprusside:

- A direct-acting arterial and venous vasodilator, is the treatment of choice for virtually all hypertensive crises.
- It reduces BP rapidly, is easily titratable, and its action is short-lived when discontinued.
- ***Dosage*** - (mix 50mg in 250ml of D5%= 200mcg / ml; 10mcg / min = 3 ml / hr), start at 0.5mcg / kg / min and titrate until the desired blood pressure has been achievedor maximal dose is reached, which ever comes first. Average effective dose is 3mcg / kg / min (range from 0.5-8mcg / kg / min). Stop if marked response not obtained with max. dose in 10 minutes.
- ***Contraindications*** are severe coronary disease, advanced hepatic or renal insufficiency.
- Therapy for more than 24 hours, in high doses, or in the presence of renal and hepatic insufficiency may cause thiocyanate toxicity as manifested by tinnitus, blurred vision, seizures, or delirium.
- Side effects include headache, dizziness, nausea, abdominal pain and renal impairment

b. Nitroglycerin:

- Drug of choice for moderate hypertension complicating unstable angina or myocardial infarction or when sodium nitroprusside is contraindicated.
- ***Dosage*** - (50mg in 250ml of NS or D5% = 200mcg / ml; 10mcg / ml = 3ml / hr) start at 5-10mcg / min and titrate until the desired BP is achieved or up to 200mcg / min.

c. Labetalol:

- Alpha-1 and beta blocker with beta-alpha ratio of 7:1.
- Can be given by slow boluses or continuous infusion.
- The usual precautions for beta blockers should be observed.
- ***(i) Bolus*** - IV 50 mg over 1-5 min and can be repeated every 5-10min till maximum doses of 200-300mg or until desired BP is achieved. Maximum response occur in 5-10 min and may last for up to 6 hours. Oral dosing can then be started at eg. 200mg 12hourly (max 2400mg / day).
  (ii) Infusion - Mix 200mg in 200ml of D5% and run at 1-2mg / min (1-2ml / min). When goal blood pressure is achieved, the infusion should be stopped and oral medication can be started.

- Excessive bradycardia can be countered with IV atropine 0.5-2mg in divided doses of 0.5mg.

d. Hydralazine:

- A direct arteriolar dilator, with an onset of action within 10 min after an IV dose and a duration of action of 3-8 hours.
- 5-20mg IV may be given, repeated if necessary at about 15-30min intervals, to a maximum of 50mg. Alternately it can be given as infusion (eg. 50mg of hydralazine in 500 ml of normal saline = 100mcg / ml; 50mcg / min = 30ml / hr) start with 50 mcg / min and titrate to reduce the BP gradually (usually 50-150mcg / min).
- This drug is best avoided in the presence of coronary arterial disease because of reflex tachycardia.

e. Esmolol:

- This is a relatively cardioselective beta blocker with a very short duration of action, used intravenously for the short term treatment, particularly in the perioperative period.
- Dilute 2.5g in 250ml of normal saline or 5% dextrose solution to a concentration of 10 mg / ml.
- A ***loading dose*** of 500mcg / kg / min for 1 min should be given followed by ***maintenance*** dose starting at a dose of 50mcg / kg / min and titrate within a range of infusion of 50-200 mcg / kg / min.
- Usual precautions for beta blockers should be observed.

4. Subsequent therapy:

- Investigate for possible underlying causes.
- If parenteral agents are used initially, oral medications should be administered often in combination shortly thereafter to facilitate weaning from parenteral therapy (over 1-2 days).

_ ATRIAL FIBRILLATION

A. Causes

1. ***Common*** - Ischaemic heart disease, mitral valve disease (commoner in stenosis), thyrotoxicosis, hypertension.

2. ***Less common*** - cardiomyopathy, pericarditis, sick sinus syndrome, atrial myxoma, endocarditis, chronic lung disease, atrial septal defect, acute alcohol intoxication, WPW syndrome, digoxin toxicity and lone AF.

B. Clinical Features

- May be either chronic or paroxysmal.
- Irregularly irregular pulse, S1 of variable intensity, pulse deficit (rate at apex is greater than at radial artery).
- ECG: chaotic baseline with no P waves, irregularly irregular but normally shaped QRS complex (unless concomitant BBB or preexcitation syndrome) at a rate of 160-200 / min. AF with regular ventricular response may suggest digoxin toxicity.
- Complications of atrial fibrillation are hypotension, cardiac failure, systemic embolism and troublesome palpitations.

C. Investigations

- BUSE, ECG, CXR, cardiac enzymes, thyroid function, calcium and Echo.

D. Treatment

Aims of therapy:

- ***Control of the ventricular rate using AV node blocking drugs*** (digitalis, beta blockers, calcium channel blockers and occasionally amiodarone).
- ***Reversion to sinus rhythm*** using membrance stabilizing agents [(class 1a - quinidine, procainamide, disopyramide), class 1c (propafenone, flecanide) and class III (sotalol, amiodarone)] or cardioversion.
- ***Prophylatic therapy*** to prevent recurrence.
- ***Anticoagulation*** to prevent embolization.

1. **Emergency synchronised cardioversion** is required in patients with rapid ventricular response (VR >200 / min) and acute haemodynamic deterioration ***(eg. patients with angina, hypotension, dyspnoea, or heart failure).***
   - If initial cardioversion is unsuccessful, ***procainamide or amiodarone*** can be given to facilitate further cardioversion attempts.
   - Do not attempt to cardiovert patients with known chronic AF & a known progressive cause (eg. MS), in which case, rapid rate control with drugs should be achieved.
   - Patients undergoing emergency cardioversion should receive anticoagulant therapy for 2-3 weeks after conversion unless there is a contraindication (anticoagulation may not be necessary if AF is <24-48 hr duration).

2. **Haemodynamically stable acute AF and Chronic AF**:

- The aim is to control ventricular rate using AV node blocking agents such as digitalis, beta blockers, calcium antagonists or amiodarone.
- In patients with ***normal heart*** clinically and on echocardiography, either ***digoxin, beta-blockers, verapamil /diltiazem or amiodarone*** can be used. If sick sinus syndrome is suspected as a cause, digoxin and drugs which exaggerate AV conduction delay should be avoided.

- In patients with ***LV dysfunction***, if
  a. ***EF <40%***, ***digoxin or amiodarone*** are the drugs of choice.
  b. ***EF >40%***, ***digoxin +/- beta blockers or amiodarone*** can be used.

a. Digoxin:

- ***Loading dose:*** Either IV 0.25-1.5mg over 24 hour (0.5mg in 50ml of NS or D5% over 1-2hrs followed by 0.25mg iv every 2-4 hours until adequate response occurs or total dose of 0.02mg/kg or 1.5mg)

  or

  orally, 0.75-1.5mg over 24 hr (eg. 0.25-0.5mg tds for 1 day, bd for 1 day) if patient has not taken digoxin for the past 1-2 weeks.
- For patients who have been taking digoxin within 1 week, a dose of 0.125mg IV or oral can be given followed by 0.125mg, if needed, after 2 hrs followed by maintenance.
- ***Maintainance dose*** is 0.0625-0.5 daily, usually 0.25mg daily (Lower doses eg. 0.0625mg should be used in elderly and in patients with renal impairment).
- In some patients, digoxin fails to prevent acitivity induced tachycardia, then a small dose of beta-blockers may be needed.

b. Propanolol:

- Propanolol is useful in AF not responding to digoxin and it has a synergistic action with digoxin.
- IV 0.5-1mg/min, repeat every 2min up to total dose of 0.15 mg/kg or 10mg.

  or

  Oral propanolol 120-240mg daily in 3 divided doses.

c. Verapamil:

- Can be used as alternative or in addition to digoxin.
- IV 5-10mg over 1-2 min followed by oral dose 40-120mg tds.

d. Diltiazem:

- Useful alternative to verapamil as verapamil has high incidence of heart failure.
- 20mg or 0.25mg/kg IV over 2 min followed, if necessary, by 25mg or 0.35mg/kg IV 15 min later. Maintenance infusion of 5-15mg/h thereafter.
- Oral maintenance of 60-120mg 3 times daily should then be given.

e. Amiodarone:

- Amiodarone is also used in the treatment of atrial fibrillation with rapid conduction that causes haemodynamic embarrassment to convert AF to sinus rhythm because of its safety in patients with poor left ventricular function and the relatively low incidence of ventricular arrhythmias. Even in those patients who did not convert to sinus rhythm, a slower heart response can be achieved compared to digoxin.
- IV: ***Loading dose*** of 300-600mg (5-10mg / kg) in 250ml of D5% over 2 hrs (may be given in 100 ml if fluid restriction) and it may need to be followed by 300-600mg in 250ml D5% over 24 hrs (ie. 5-10mg / kg / day to a daily maximim dose of 1.2g). The infusion can be continued for several days (max 2-3 weeks) before changing to oral amiodarone.
- In emergency, the loading dose can be put in 100ml and run over 10 mins.
- ***Transition to oral therapy:*** 200mg 3 times daily for 1 week reduced to 200mg twice daily for a further week then maintenance dose.
- ***Maintenance:*** Usually 200-300mg daily.

 # Digoxin and verapamil are strictly contraindicated with WPW in atrial fibrillation.

3. Elective conversion to sinus rhythm:

- An attempt should be made to convert all patients with ***AF present for < 6-12 months, and when the left atrium is not enlarged (<45mm).*** Cardioversion is less likely to be successful if AF has been present for over a year, left atrial size is >45 mm, and untreated conditions are present (eg. thyrotoxocosis, valvular heart disease and heart failure).
- ***Pharmacological conversion*** should be attempted first.
- ***Class 1a*** - (quinidine, procainamide, disopyramide), ***Class 1c*** (propafenone, flecanide) and ***Class III*** (sotalol, amiodarone) drugs can be used to restore sinus rhythm but ventricular response should be controlled first. Class IA and IC drugs should be avoided in patients with left ventricular hypertrphy, with coronary artery disease and with a previous infarct.
- If atrial fibrillation persists, digitalis should be withheld for 24h, and then ***DC cardioversion*** (start with 100J) should be attempted (refer to section on cardioversion).
- In elective cardioversion (electrical or pharmacological), ideally, the patient should receive a 4 week course of oral anticoagulation before conversion and for 4 weeks after conversion. Cardioversion can also be attempted early if transesophageal echocardiography does not show evidence of left atrial thrombi.

4. Prophylatic therapy to prevent recurrece of AF:

- If sinus rhythm is restored, ***dual therapy*** with both an AV node blocking drug and a membrance stabilizing agent (Class IA, IC or III) is recommended to prevent recurrence (except for sotalol and amiodarone, which have both properties when monotherapy is adequate).

- If recurrences cannot be prevented, therapy is directed toward controlling the ventricular rate.
- ***Sotalol and amiodarone*** may be preferred in ***paroxysmal AF.***
- ***Permanent pacemaker:*** High rate atrial pacing may inhibit AF.
- ***Radiofrequency catheter ablation*** may offer cure for selected cases.

5. Prophylaxis for embolic phenomenon:

a. Acute AF:

- IV heparin should be given to all patients except those with AF of <24-48hrs.

b. Chronic AF:

- Guidelines are summarized as below:

Age	Risk Factors*	Recommendations
< 60	Present Absent	Warfarin with INR 2-3 Aspirin or nothing
60-75	Present Absent	Warfarin with INR 2-3 Warfarin or Aspirin
> 75#		Warfarin with INR 2-3 or Aspirin

* ***Risk factors:*** *Previous TIA or stroke, hypertension, DM, coronary artery disease, mitral valve disease, prosthetic heart valves and thyrotoxicosis*

\# ***Age >75,*** *little data available, has increased risk of major haemorrhage from warfarin, continue if already on & tolerating. Otherwise, consider patient's long-term outlook, concomitant medical problem and etc.*

6. Footnotes:

_ ***Vaughan Williams' Classification of antiarrhythmic drugs.***

Class	Mechanism of Action	Drugs
I	Membrane-depressant drugs that reduce the rate of entry of sodium into the cell.	
Ia	Lengthen the action potential	Quinidine Procainamide Disopyramide
Ib	Shorten the action potential	Lignocaine Mexiletine Tocainide Phenytoin
Ic	Do not affect the duration of action potential	Flecainide Propafenone

II	Beta-adrenergic blocking drugs which prevent the effects of catecholamines on the action potential	Propanolol Metoprolol
III	Prolong the action potential and do not affect sodium transport through the membrane	Amiodarone Sotalol Bretylium
IV	Non-dihydropyridine calcium antagonist that reduce the plateau phase of the action potential	Verapamil Diltiazem
Others		Adenosine Digoxin

_ ATRIAL FLUTTER

A. Causes

- Atrial flutter rarely occurs without heart disease eg. rheumatic and ischaemic heart disease, cardiomyopathy, thyrtoxicosis, valvular disease, septal defect and digoxin toxicity.

B. Clinical Features

- Atrial flutter is a rhythm that originates from a small area within the atria.
- ***ECG:*** P waves are replaced by flutter waves resulting in 'saw-tooth',or 'corrugated' pattern. Flutter may sometimes be obscured by the T wave. Carotid sinus massage will usually slow the ventricular rate and flutter waves may then be more obvious. Ventricular rate is often regular but may vary depending on the degree of A-V block present and is a fraction of atrial rate 1:2, 1:3, etc. Rarely, 1:1 conduction occurs. Atrial rate is usually between 250-350 / min.

When ventricular rate is 150/min, suspect atrial flutter with 2:1 block until proven otherwise.

C. Managment

1. **DC cardioversion** in haemodynamically unstable patients, patients with symptoms and signs of ischaemia, VR >200 / min, known or suspected to have WPW syndrome. Synchronized DC shock of 25-50J is usually adequate.

2. **Control of the ventricular rate using AV node blocking drugs *(digitalis, beta blockers,calcium antagonists or amiodarone):***

- Digoxin often converts atrial flutter to AF and slows the ventricular response.
- Beta-blockers (eg. IV propranolol or esmolol, oral propranolol or metoprolol) slows the ventricular response rate by causing AV blockade.
- IV verapamil or diltiazem may reduce the ventricular response but conversion to sinus rhythm rarely occurs.
- IV amiodarone has also been shown to slow the ventricular rate as effectively as digoxin.
- Adenosine produces transient AV block and can be used to reveal flutter waves if the diagnosis of the arrhythmias is in doubt but it generally will not terminate the atrial flutter and can provoke atrial fibrillation.

Verapamil and digoxin are contraindicated in patients with WPW syndrome presenting with atrial flutter or AF.

3. **Reversion to sinus rhythm** using membrance stabilizing agents ***[(class 1a - quinidine, procainamide, disopyramide), class 1c (propafenone, flecanide) and class III (sotalol, amiodarone)] or DC cardioversion:***

- Class I or III drugs should not be used unless the ventricular rate during atrial flutter has been slowed with digitalis, calcium antagonist or beta blockers.
- Class I and III drugs should be discontinued if flutter remains.
- Class IA and IC drugs should be avoided in patients with left ventricular hypertrophy, with coronary artery disease and with a previous infarct.
- DC cardioversion is very effective for atrial flutter with as little as 25-50J of energy.

4. Prophylatic therapy to prevent recurrence of flutter:

- ***Dual therapy*** with both an AV node blocking drug and a membrance stabilizing agent is recommended except for sotalol and amiodarone, which have both properties.
- If recurrences cannot be prevented, therapy is directed toward ***controlling the ventricular rate*** when the flutter does recur, with digitalis alone or in combination with beta blockers or calcium antagonists.

5. Anticoagulation:

- There is currently no clear evidence of increased risk of systemic embolism in ***acute atrial flutter,*** and anticoagulation is not generally recommended.
- In ***chronic atrial flutter***, anticoagulation is recommended since transient runs of atrial fibrillation are common in these patients.

6. Catheter ablation of flutter circuit:

- This technique should be considered in patients refractory to drug therapy.

_ SUPRAVENTRICULAR TACHYCARDIA, PAROXYSMAL

- A condition in which the heart rate suddenly increases to 100-250 beats / min and 1:1 A-V conduction is maintained.
- SVT is most often due to reentry, generally within the AV node or involving an accessory pathway, although sinus node reentry, intra-atrial reentry, and SVT due to enhanced automaticity can also occur.
- SVT often occurs in patients with a healthy heart, but may occur in patients with organic heart disease and with WPW syndrome.
- The arrhythmias is of sudden onset, and may be associated with sensation of rapid palpitations in the chest or throat, dyspnoea, light headedness, or chest pain. Cardiac failure may develop. Termination of the arrhythmia, whether spontaneous or with treatment, is sudden.

A. Type and ECG diagnosis of SVT

	Type	Incidence	ECG manifestations
1.	***AV node reentry***	60%	Retrograde P wave most frequently buried in QRS or with

			short RP (RP <50% RR interval), Negative P wave in II, III, AVF.
2.	***SVT with accessory pathway (i) Concealed* (ii) Manifest****	25%	Retrograde P wave with short RP (RP<50% RR interval), negative P wave lead I.
3.	***Intra-atrial re-entry***	5%	Positive P wave in II, III, AVF (indicating antegrade atrial activation), RP>50% RR interval.
4.	***Sinus node re-entry***	rare	P wave morphology indentical to sinus rhythm (RP>50% RR).
5.	***Automatic atrial tachycardia***	5%	Positive or negative P wave in II, III, AVF depends on the location (RP>50% RR interval).

* ***Manifest accessory pathway*** (AP) conducts anterogradely during sinus rhythm, and characteristic delta waves and short (<0.12s) PR intervals are observed in the ECG, reflecting ventricular preexcitation.
Concealed AP only conducts retrogradely, and ventricular preexcitation is not present during sinus rhythm.

B. Management

I. Acute therapy

1. **Immediate cardioversion (50J)** is required in patients with acute haemodynamic deterioration ***(eg. patients with angina, hypotension, dyspnoea, or heart failure)***

2. **Vagal stimulation** may terminate some SVT (AV node dependent tachycardia) by increasing parasympathetic tone while inhibiting sympathetic outflow.
- ***Carotid sinus massage***: The patient should be supine with an IV line in place and the ECG monitored. Before massage, the carotid vessels should be auscultated for bruits, and carotid massage is rarely so essential that it needs to be done even if bruits are heard. The right carotid sinus should be massaged first, for no more than 10 seconds. If this is ineffective, the left carotid should be massaged. The left and right carotids should never be massaged simultaneously.
- ***Valsalva maneuver*** may also be helpful.

3. **Drugs**:
- In patients with ***normal heart***, if no response is obtained from vagal maneuvers, ***IV verapamil or adenosine*** is indicated. Verapamil can cause hypotension and is contraindicated if systolic BP is <90mmHg. Adenosine has the advantage of not causing hypotension.
- In patients with ***heart failure or left ventricular dysfunction***, ***digoxin*** is the drug of choice. ***Adenosine*** can also be used.

- In patients with AMI, IV ***beta-blockers*** especially short-acting is advisable if there is no contraindication.

a. Adenosine:

- Causes inhibition of sinus node automaticity, depression of AV node conduction, and prolongation of AV nodal refractoriness.
- ***Contraindicated*** in second or third degree AV block, sinus node disease, known hypersensitivity to adenosine, asthma, COPD with theophylline usage.
- Rapid IV bolus 6 mg. Onset of action is 15-30 secs and the duration of action only 1-2 minutes. A second bolus injection of 12 mg is repeated 2-5 minutes after the first if the arrhythmia persists or recurs. Another 12mg dose may be given in 2-5 mins, if required.

b. Verapamil:

- 5 mg IV over 2-3 mins with monitoring of cardiac rhythm and BP (Use 2.5mg if LV function is believed to be slightly impaired). If arrhythmia persisted, additional 2.5-5mg dose can be given 10 minutes after the first dose.
- Pretreatment with calcium chloride or calcium gluconate (10ml of a10%solution over 5-10 mins) before verapamil bolus may prevent many of the hypotensive effects of verapamil without antagonizing the negative dromotropic effects.
- If sinus arrest or AV block occurs, give calcium chloride or gluconate and atropine (0.5-1mg IV repeated, to a total dose of 2mg, if required).
- Should be used with caution in the elderly and is ***contraindicated*** in those with hypotension (<90mmHg) , high-degree AV block, heart failure of all grades, LV dysfunction (particularly with cardiomegaly or EF <40%), sick sinus syndrome, suspected digoxin toxicity, beta blockade, concomitant use of disopyramide or amiodarone, wide QRS tachycardia (unless identical complexes of intraventricular conduction delay seen on previous ECG while in sinus rhythm), and atrial flutter or fibrillation complicating WPW syndrome

c. Diltiazem:

- Useful alternative to verapamil as verapamil has high incidence of heart failure.
- 20mg or 0.25mg / kg IV over 2 min followed, if necessary, by 25mg or 0.35mg / kg IV 15 min later. Maintenance infusion of 5-15mg / h thereafter.

d. Propanolol:

- IV 0.5-1mg / min, repeat every 2min, until rhythm converts or up to total dose of 0.15 mg / kg.

e. Digoxin:

- Digoxin 0.5mg IV with repeat doses of 0.25mg in 1-2hrs until a response occurs or total dose of 0.02mg/kg or 1.5mg has been achieved.

f. ***Quinidine, procainamide and flecanide*** may also be considered.

4. **Elective cardioversion or rapid atrial pacing** may be required if the preceding techniques prove unsuccessful.

II. Prophylaxis against recurrence

- Decisions regarding ***prophylactic therapy*** should be based on the SVT mechanism, frequency of episodes, underlying heart disease, and symptoms.
- Prophylactic therapy is generally needed only in patients with bothersome episodes (eg. occurring several times annually).
- This can be done by the use of drugs that act primarily on the ***antegrade slow pathway (eg. digoxin, B-blockers, calcium channel antagonists) or on the fast pathway (eg. quinidine-like agents, flecainide, propafenone, and amiodarone).*** Generally, the former group is preferred because the risk-benefit ratio is more favourable.
- During ***acute attacks*** outside the hospital**,** if vagal maneuvers fail, (if WPW and structural heart disease are excluded) one tablet 80mg verapamil may be taken. An additional 80mg tablet may be taken 1 hour later if the arrhythmia persists. If this is not effective, the patient is advised to go to the emergency room.
- ***Electrophysiologic study and Radiofrequency ablation*** offer a chance of cure for SVT.

_ VENTRICULAR ECTOPIC (PVC)

- Occurs in normal subjects and patients with heart disease.They are due to intraventricular reentry or disturbances in automaticity.
- They are exacerbated by electrolyte imbalance, hypoxia, acid-base imbalance, endocrine disorders such as thyrotoxicosis, and a variety of medications eg. digitalis, phenothiazines, tricyclic antidepressants, and antiarrhythmias. Tobacco smoking and beverages such as tea, coffee and alcohol can also induce or exacerbate PVCs.
- In patients without heart disease, PVCs have not been shown to be associated with any increased incidence in mortality or morbidity.
- ***ECG changes:*** Wide and bizarre premature QRS(>0.12s). T wave is usually large and opposite in direction to the major deflection of the QRS. QRS is usually not preceded by a premature P wave.
- The following patterns of PVCs in the setting of AMI may precede ventricular tachycardia or fibrillation, and require urgent treatment particularly in the first 24 hours (the Lown`s classification).
  (i) Multifocal (ii) Frequent, >5/min (iii) occur in runs of 2 or more (iv) R-on-T.

A. Management

1. Indications for treatment of PVCs

- In the setting of AMI, most physicians would treat PVCs especially if the risk of VT or VF is high, ie. ***>5 PVCs/min, multifocal PVCs, coupled PVCs, runs of VT or R-on-T phenomenon.***
- In patients with chronic ectopics, the following factors should be considered in deciding whether a patient needs to be treated: ***(i) the underlying heart disease (ii) the nature of the ectopic (iii) the presence or absence of symptoms (iv) the potential side effects of oral antiarrhythmic therapy.***
- In the absence of cardiac disease, isolated asymptomatic PVCs, regardless of configuration and frequency, need no treatment. The underlying cause of the PVCs and the precipitating factors should be identified and treated.

2. Therapy:

a. Acute suppression of PVCs can be achieved with IV lignocaine, procainamide, amiodarone, disopyramide, bretylium or beta-blockers.
- Please refer to treatment of VT for dosages.

b. Chronic suppression of PVCs may be achieved by using class I agents, amiodarone or beta-blockers.
- Generally, a trial of ***beta-blockers*** (eg. metoprolol 50-100 mg bd or propranolol 10-40 mg tds / qid) should be given; if symptoms persist substitution with or addition of ***mexiletine*** (200 mg tds / qid) may be advisable. ***Amiodarone*** (200 mg tds for 1week, then 200 mg for another week followed by a maintenance of 200 mg daily) or ***sotalol*** (80 mg in 1-2 divided doses increased gradually at intervals of 2-3 days to usual dose of 160-320 mg daily in 2 divided doses) should be considered if symptoms persist despite beta-blocker and mexiletine.

_ VENTRICULAR TACHYCARDIA

- A regular ventricular rhythm with 3 or more broad QRS complexes and at a rate between 100-200 beats / min.

A. Causes

- Ischaemic heart disease, AMI, cardiomyopathy, prolonged QT syndrome, mitral valve prolapse, drug toxicity eg. digoxin, and metabolic disorders. It may occur in normal individuals.

B. Clinical features

1. ***Haemodynamic instabilities*** eg. hypotension, cardiogenic shock, and pulmonary oedema. A small percentage of patients may be asymptomatic.
2. ***ECG characteristics:***
   (i) three or more wide QRS complexes (ii) rate greater than 100 (iii) rhythm usually regular with occasional beat-to-beat variation (iv) QRS axis usually constant (v) ST and T wave changes in a direction opposite to the major QRS deflection.

- Classified as ***nonsustained*** or ***sustained***:
  Sustained VT is defined as lasting longer than 30 s or associated with immediate haemodynamic collapse.
- It is important to distinguish SVT with aberration or intraventricular conduction from VT because tha clinical implications and management of these arrhythmias are different.

	Features favouring VT include the following:
a.	QRS duration _0.14 s.
b.	Sinus capture beats with narrow QRS morphology.
c.	AV dissociation.
d.	Fusion beats.
e.	Concordance of the QRS pattern in all precordial leads (ie. all positive or all negative deflections - a totally negative precordial concordance is always VT).
f.	Predominantly negative QRS complexes V4-V6 or in one or more of V2 to V6.
g.	Morphology in V6: QS or rS.
h.	Morphology in V1: if positive, 'left rabbit ear' taller than the right.
#	**IF IN DOUBT, VT SHOULD BE DIAGNOSED.**

C. Management

1. Acute therapy:

- ***In haemodynamically unstable patients***, immediate cardioversion is indicated. IV lignocaine (or procainamide or bretylium when appropriate) should be administered concomitantly.

- ***In stable patients,*** the following antiarrhythmias should be given. Generally, no more than 2 drugs should be used. If patients deteriorate, immediate electical cardioversion is indicated.

  a. Lignocaine: Drug of choice.
  - ***IV bolus*** 50-100mg (1mg/kg), repeats as necessary at 0.5mg/kg at intervals of 10 min to a total dose of 3mg/kg and followed by infusion of 4mg/min for 1hr, 3mg/min for 1 hr, and 1-2mg/min for ***maintainance*** (eg. mix 2g in 500ml of NS or D5%= 4mg/ml; 1mg/min = 15ml/hr).

- Decrease the dose by 50% in the presence of AMI, acute pulmonary oedema or shock & in those patients over 70 years due to reduced volume of distribution.

- ***Features of toxicity:***
  CNS: circumoral paraesthesias, transient auditory disturbances, drowsiness, delirium, muscle twitching, and seizures.
  Cardiac: sinus bradycardia, AV block, depression of myocardial contractility.

b. Procainamide: can be given if lignocaine is ineffective.

- The ***loading dose*** is given as 100mg at 25-50mg / min q5min until arrhythmia terminates or a maximum of 15mg / kg (or 1g) has been achieved or when adverse effects develop (hypotension or QRS duration increases by 50% of the original width). ***Maintenance*** of 1-4mg / min is then given (mix 2g in 500ml of D5% or NS = 4mg / ml; 1mg / min = 15ml / hr).
- ECG and BP monitoring are essential.
- ***Toxicity:*** sinus arrest, AV block, ventricular arrhythmia and hypotension. Prolongation of QT interval and QRS widening are ECG signs of toxicity.

c. Amiodarone:

- May be used as alternative to procainamide.
- IV: ***Loading dose*** of 300-600mg (5-10mg / kg) in 250ml of D5% over 2 hrs (may be given in 100 ml if fluid restriction) and it may need to be followed by 300-600mg in 250ml D5% over 24 hrs (ie. 5-10mg / kg / day to a daily maximim dose of 1.2g). The infusion can be continued for several days (max 2-3 weeks) before change to oral amiodarone.
- In emergency, the loading dose can be put in 100ml and run over 10 mins.

 # These agents can be continued for several days if necessary.
 # If the above measures fail and VT persists, synchronised DC shock is preferred to further antiarrhythmics.
 # Urgent BUSE, Se Calcium, Se magnesium, ABG should be sent. Any electrolyte abnormality should be corrected. Severe acidosis (PH <7.2) should also be corrected.
 # Consider magnesium sulphate (1-2g in 50ml over 15 min) if hypomagnesaemia is suspected especially if patient is on diuretics or if there is history of alcohol intake.

2. Chronic therapy:

- Once VT has been terminated, further episodes can be prevented by continued use of ***suppressive drug***, eg. ***class I agents, ß-blocker and amiodarone*** in a subgroup of patients without obvious precipitating factors.

- ***Electrophysiologic study*** would be helpful. The patient can be given antiarrhythmic drug therapy, after which electrophysiologic study can be repeated to assess drug efficacy.
- If drug therapy suppresses VT, it is continued indefinitely. However, if drug therapy is unsuccessful, the patient should be considered for implantation of a defibrillator.
- ***Radiofrequency ablation*** is also possible for some forms of VT.

_ TORSADES DE POINTES

- Torsades depointes arises when ventricular repolarization is greatly prolonged (long QT interval; often > 0.60 s).

A. Causes

1 ***Congenital syndromes:***
Jervell-Lange-Nielsen (AR)
Romano-Ward (AD)

2 ***Electrolyte abnormalities:***
Hypokalaemia
Hypomagnesaemia
Hypocalcaemia

3 ***Drugs:***
Quinidine (and other class Ia antiarrhythmics)
Amiodarone (and other class III)
Amitriptyline (and other tricyclic antidepressants)
Chlorpromazine (and other phenothiazines)
Terfenadine and astemizole
Terodiline
Erythromycin

4 ***Poisons***
Organophosphate insecticides

5 ***Miscellaneous***
Bradycardia
Mitral valve prolapse
AMI
Prolong fasting and liquid protein diets
CNS diseases

B. Clinical Features

- This arrhythmia is usually short in duration and spontaneously reverts to sinus rhythm. It may give rise to presyncope or syncope and occasionally convert to ventricular fibrillation and cause sudden death.
- Characterized on the ECG by rapid, irregular, sharp complexes that continuously change from an upright to an inverted position. ECG shows a prolonged QT interval between spells.
- Normal QTc = $\frac{QT}{RR\ interval}$ = 0.38-0.46s.
- Eyeballing of QT - If the QT interval is longer than half its corresponding R-R interval, then suspect the QT is prolonged.

C. Management

1. Acquired prolonged-QT:

- Any ***precipitating factor*** should be identified and removed.
- Any ***electrolyte disturbance*** is corrected eg. K and Mg deficiency.
- ***Causative drugs*** are stopped.
- Sustained arrhythmia in the presence of haemodynamic compromise should be treated with ***DC cardioversion.*** In stable patient, cardioversion should be a last resort because the rhythm will likely recur or degenerate to VF.
- ***Magnesium sulfate,*** is highly effective in the treatment and prevention of drug-induced torsades de pointes. Initial dose of 1-2g IV bolus over 5-10 mins, followed by an infusion of 1g / hour for 4 hour, if successful, is currently considered first-line drug therapy ($MgSO_4$ 1 g = 4 mmol of elemental Mg). Use cautiously in patient with impaired renal function.
- ***Temporary transvenous pacing*** is the safest and most effective method of management because the heart rate can be quickly and easily controlled for long periods. It should be attempted if magnesium is unsuccessful. Either atrial or ventricular pacing can be used.
- ***Intravenous isoprenaline*** (to shorten QT interval by increasing HR), is sometimes used if pacing is not readily available. An infusion rate of 2-20mcg / min can be used (2 mg is added to 500ml D5% or NS = 4mcg / ml) and infusion should be titrated to maintain HR between 100-120 bpm (Isoprenaline is CI for congenital Long QT syndrome).
- Isoprenaline is ***contraindicated*** in AMI, angina, or severe hypertension.

2. Congenital prolonged-QT:

- For patients who have the idiopathic long Q-T syndrome but do not have syncope, complex ventricular arrhythmias, or a family history of sudden cardiac death, no therapy is recommended.
- Patients with congenital QT prolongation are best managed with ***beta-blockers +/- Class IB agents.*** Class IB agents, eg. phenytoin, mexilitine have

a role if beta blockers are contraindicated (Isoprenaline is CI for congenital Long QT syndrome).

- Resistant cases are managed with ***permanent pacing plus beta-blockers*** *or* ***left stellate ganglionectomy.***
- ***An implantable cardioverter defibrillator*** should be considered if the above measures failed.
- Remember Class IA and Class III (and possibly Class IC) aggravate torsades de pointes.

_ WOLFF-PARKINSON-WHITE (WPW) SYNDROME

1.41

Cardiology

- Most common form of ventricular preexcitation and is due to an accessory pathway (Kent bundle) connecting the atria and ventricles.Two types are seen:
  (a) ***Type A*** with the bypass situated on the left of A-V ring. ECG shows upright QRS in right precordial leads (tall R waves in V1-V2).
  (b) ***Type B*** with the bypass situated on the right of the A-V ring (negative QRS in V1 and V2 on ECG).
- Majority of patients have normal hearts but WPW has been associated with Ebstein's anomaly, hypertrophic cardiomyopathy, and others.
- WPW syndrome as a term is to be used only when there is demonstrated supraventricular tachycardia occuring with the accelerated conduction abnormality.

	Type of conduction in WPW syndrome	**ECG changes**
1.	***Sinus rhythm*** - anterograde conduction occurs over both AV node and accessory pathway(AP)	A short PR interval (<0.12s) with widened QRS. Upslope of R wave is slurred and designated a delta wave.
2.	***Orthodromic SVT***- AV node conducts antegradely and AP retrogradely. (95%)	Retrograde P wave with short RP and negative P wave lead I. Narrow QRS complexe. No delta wave is seen.
3.	***Antidromic SVT*** - AV node conducts retrogradely and AP antegradely.(5%)	Widened QRS complex with pronounced delta wave.
4.	***Atrial flutter*** or ***AF*** conducting	Ventricular responses may be unusually rapid and may cause VF since the AP does not have the same decremental (prolonged AV conduction with increased HR) properties as the AV node.

A. Management

I. Acute therapy

1 Narrow complex WPW tachycardia or orthodromic SVT:

- Can be treated like other cases of reentrant SVT as described before.
- After vagal maneuvers, ***adenosine*** (6-12mg), IV ***verapamil*** (5-10mg) or ***diltiazem*** (15-20mg) is the initial treatment of choice. ***Procainamide*** is another pharmacologic option that is usually effective. ***Digoxin should be***

avoided and beta-blockers are usually ineffective. Atrial fibrillation can occur after drug administration, particularly adenosine, with a rapid ventricular response. Therefore, an cardioverter-defibrillator should be available.

2 Wide-complex WPW tachycardia (antidromic, atrial flutter or fibrillation):

- Those haemodynamically unstable represents a medical emergency and should be treated by ***immediate cardioversion.***
- Those stable haemodynamically can be treated acutely with IV ***procainamide*** (10-15mg/kg given as 50mg/min).
- IV ***amiodarone*** in the usual recommended doses is also effective but may precipitate VF.
- ***DIGOXIN AND VERAPAMIL ARE STRICTLY CONTRAINDICATED IN THIS SETTING.*** Beta blockers are usually ineffective.

B. Chronic therapy

1. Asymptomatic patients:

- Generally do not require empiric therapy.
- ***EPS (Electrophysiologic study)*** may be indicated when ***i) there is family history of WPW, with or without sudden death ii) he or she has a high-risk occupation (eg. an airline pilot).***

2. Symptomatic patients:

- Most symptomatic patients would probably require electrophysiologic testing to assess antegrade pathway conduction.

a. Medical therapy:

- ***Class Ia or Ic agents, amiodarone or sotalol*** may be effective for chronic therapy in both narrow complex and wide-complex tachycardia.
- Chronic therapy with nodal blocking agents in narrow complex tachycardia in WPW carries a small risk of promoting a rapid ventricular response to AF and susequently VF.

b. Ablation of accessory pathways by either radiofrequency or surgical means provide an alternative to medical therapy.

- Indications: ***patients with frequent symptomatic arrhythmias that are not fully controlled by drugs, in patients who are drug intolerant, in those who do not wish to take drugs, or WPW syndrome who is found to have life-threatening conduction capability via the accesory pathway.***
- Treatment of choice if easily available.

_ ATRIOVENTRICULAR (AV) BLOCK

A Clinical classification

1. **First-degree AV block:** Delay in AV conduction.

2. **Second-degree AV block:** Intermittent AV conduction - some atrial impulses reach the ventricles and others are blocked.

3. **Third-degree AV block:** Complete interruption in AV conduction.

- AV blocks can be further divided into nodal and infranodal blocks. Nodal blocks are usually due to reversible depression of conduction, generally do not have a serious prognosis. Infranodal blocks are usually due to organic disease of the His bundle or bundle branches, they generally have a slow and unstable ventricular escape rhythm pacing the ventricles, and they may have a serious prognosis.

B. First-Degree AV Block

- ***Causes:*** Increased vagal tone, digitalis toxicity, acute inferior MI, myocarditis and occasionally in normal hearts.
- ***Clinical:*** Asymptomatic.
- ***ECG:*** PR interval of >0.20s.

- ***Management:*** None is required.

C. Second-Degree Mobitz I (Wenckebach) AV Block

- This type of block almost always occurs at the level of the AV node and is often due to reversible depression of AV nodal conduction. It is often transient.
- ***Causes:*** Acute Inferior MI, digitalis toxicity, myocarditis and occasionally normal individual.
- ***ECG:*** Progressive PR interval prolongation prior to block of an atrial impulse. PR interval of the first conducted impulse is shorter than the last conducted atrial impulse prior to the blocked P Wave (When R waves appear in groupings of twos or threes, suspect second degree AV block).
- ***Management:*** Specific treatment is not necessary unless slow ventricular rates produce signs of hypoperfusion. Then 0.5mg of atropine IV is given, repeated every 5 min as necessary until the total dose of 2mg.

D Second-Degree Mobitz II AV block & High-grade block

- Type II blocks & high-grade blocks imply structural damage to the infranodal conducting system, are usually permanent, and may progress suddenly to complete heart block.
- ***Causes:*** Similar to first degree heart block.
- ***ECG:*** Conduction fails suddenly and unexpectedly without a preceding change in PR intervals, and often associated with a prolonged QRS duration. May have a constant AV block ratio (high grade block), eg. 2:1, 3:1 etc, where P waves are 2 and 3 times more frequent than QRS complexes.
- ***Management:*** In the presence of symptoms of hypoperfusion, atropine or isoprenaline can be used. However, isoprenaline is potentially hazardous in the setting of AMI or digitalis toxicity. Most cases will require permanent transvenous cardiac pacing.

E. Third-Degree (Complete) AV Block

- There is no AV conduction. The ventricles are paced by an escape pacemaker at a rate slower than the atrial rate. Can occur either at nodal or infranodal level.
- ***Causes:***
  - ***(i) Nodal***- Inferior MI, congenital block.
  - ***(ii) Infranodal*** - Acute anterior MI, idiopathic fibrosis.

- ***ECG:*** Regular P waves, completely dissociated from QRS complexes, PR interval varies. QRS may be normal or widened.
  - ***(i) Nodal*** - Narrow QRS complexes with a ventricular rate of 40-60.
  - ***(ii) Infranodal*** - Widened QRS complexes with a ventricular rate of <40.
- ***Management:***
  - ***(i) Nodal third-degree AV Block*** - as for second degree Mobitz I AV block.
  - ***(ii) Infranodal third-degree AV Block*** - Usually requires pacemaker. Isoprenaline can be used temporarily to accelerate the ventricular escape rhythm.

_ CARDIOVERSION AND DEFIBRILLATION

- **Definition:** ***Cardioversion*** refers to the use of electrical energy to revert cardiac arrhythmias other than VF. The electrical energy is delivered synchronized to the R wave of the surface ECG. This minimizes precipitation of VF. ***Defibrillation*** refers to the application of sufficient electrical energy to the heart in VF.

A Indications for Cardioversion

- ***In the presence of haemodynamic compromise, when medical cardioversion has failed or as initial form of therapy, in:***

1. Atrial flutter.
2. Atrial fibrillation when present for <6-12mon.
3. Supraventricular tachycardia.
4. Ventricular tachycardia.

B Relative contraindications

1. ***Atrial fibrillation*** of > 6 months duration, associated with thyrotoxicosis, sick sinus syndrome, uncorrected precipitating cause (cardiomyopathy, myocarditis / pericarditis, markedly enlarged left atrium), and a slow ventricular rate in the abscence of drugs.
2. ***Digoxin toxicity*** - Cardioversion has been shown to be hazardous in the presence of digoxin toxicity, but is safe in the patient with digoxin levels within the therapeutic range.
3. ***Severe conduction system disease*** eg. heart block.
4. ***Repeated short-lived tachycardias***.
5. ***Electrolyte and acid-base disturbance***.

C Procedures of cardioversion

a. **Consent** - Informed consent should be taken.

b. **Anticoagulation** - should be administered for up to 4 weeks before the procedure (elective cardioversion) in atrial fibrillation and may need to be continued after cardioversion.

c. **Facilities for Resuscitation** - should be available. Patient should be supine on a hard surface that can support the chest, should CPR become necessary.

IV access and ECG monitoring should be available. Where the procedure is electively performed, ensure the presence of ananaesthetic colleague.

d. **Fasting** - To minimize the risk of aspiration, patient should be fasted for ***at least 6 hrs.***

e. **Sedation** - Patient should be sedated with ***diazepam*** 5-20mg IV or ***midazolam*** 2.5-10mg IV.

f. **Paddle placement** - One paddle is placed to the right of the sternum below the clavicle, and the other to the left of the nipple with the centre over the mid axillary line. Conductive gel or gel pads should be used.

g. **Suggested energy sequences-**

VF and unstable VT	200, 200-300, 360J
Stable VT	50-100, 200, 300, 360J
AF	100, 200, 300, 360J
Atrial flutter	25-50, 100, 200, 300, 360J
SVT	50, 100, 200, 300, 360J

h. **Synchronization and cardioversion**- Before the defibrillator is activated, make sure the defibrillation is in synchronized mode (except in VF and pulseless VT) and the patient is not in direct contact with any person or metal object.

i. It is important after successful restoration of SR, to consider the need for **antiarrhythmic therapy** in order to prevent arrhythmia recurrences.

D Potential complications of cardioversion/defibrillation

1. Skin burns.
2. Aspiration pneumonia.
3. Bradycardia.
4. Asystole.
5. Ventricular fibrillation.
6. Transient hypotension.
7. Thromboembolism.
8. Pulmonary oedema.

_ CARDIAC ARREST

- There are three mechanisms for cardiac arrest:
  i) Ventricular fibrillation. ii) Asystole. iii) Electromechanical dissociation.

A Initial management of Cardiac arrest

- ***Confirm the diagnosis*** (unconscious, absent carotid or femoral pulse), check the time, start CPR and call for help.
- ***Airway:*** Extend the neck by head tilt and chin lift. Clear the airway.
- ***Breathing:*** Assess for the presence of respiration. If no spontaneous breathing, give 2-breaths of mouth-to-mouth.

- ***Circulation:*** Palpate for carotid pulse. If pulse is not present, deliver 15 chest compression at a rate of 80-100 / min. After 15 compressions, deliver 2 rescue breaths (ratio 15: 2). For 2 rescuer, compression-ventilation is 5:1.
- When help arrives, give 100% O2 via ambu-bag, ***set up IV line*** at the antecubital fossa (not at the hand or wrist) - 1000ml of ***normal saline*** should be infused and ***ECG leads*** placed**.** Carry on CPR except during ***intubation*** and ***defibrillation.*** Not more than 30s should be allotted for intubation. If intubation fails, restart compressions. Once the patient is intubated, ventilations can be given at a rate of 12-15 / min, without pausing for compressions.
- ***Subsequent management*** will depend on ECG rhythm (see section on specific arrest sequences).
- ***Prepare the following drugs:*** 10ml 1:10,000 or 1ml 1:1,000 ***adrenaline, lignocaine*** 100mg IV, 50ml ***bicarbonate*** 8.4%, ***Isoprenaline*** 2mg in 500ml 5% dextrose. If IV access fails, adrenaline, atropine, and lignocaine can be given via an ETT but double the normal IV dose.
- If cardiac arrest has persisted for more than 30 min, resuscitation is unlikely to be successful. Check for signs of brain death.
- After successful resuscitation, it is important that the patient be monitored carefully. ***Antiarrhythmic agents*** are necessary in VF or VT. Fluid balance, ABG, CVP, urine output and electrolytes need to be monitored closely and treated appropriately. Dopaminergic support may be needed.

B Specific Arrest Sequences

1. Ventricular fibrillation and pulseless ventricular tachycardia.

- Precordial thump in witnessed arrest.
- Defibrillate 200J. Check pulse, recharge, give 15 chest compressions, check monitor. (**)
- Defibrillate 200-300J.**
- Defibrillate 360J.**
- Intubation if not already.
- Adrenaline 1mg IV or ETT.
- Defibrillate 360J.**
- Administer medications of probable benefit in persistent or recurrent VF / VT.

  Medication sequence:
  - ***Lignocaine*** 1.0-1.5mg / kg IV push. Repeat 3-5 mins to maximum dose of 3mg / kg.
  - ***Bretylium,*** 5mg / kg IV push. Repeat in 5 mins at 10mg / kg up to max of 35mg / kg.
  - ***Amiodarone*** 150mg IV over 10 mins, can be repeated.
  - ***Magnesium sulfate***, 1-2g IV in torsades de pointes, suspected hypomagnesemic state, or refractory VF.

- ***Procainamide*** 30mg / min to maximum total dose of 17mg / kg in refractory VF.

 # There should be cycles of at least a further DC shock and continued CPR for one minute (approximately 10 sequences of 5:1 compression-ventilation) before each new drug is given.

- Defibrillate 360J.**With changed paddle position.
- Defibrillate 360J.**Using another defibrillator.

Note:

- Adrenaline should be repeated every 5 mins.
- Intubation is essential, however, defibrillation and adrenaline are more important initially if the patient can be ventilated without intubation.
- Value of sodium bicarbonate is questionable during cardiac arrest.
- If VF recurs after transiently converting, use whatever energy level has previously been successful for defibrillation.
- Once VF has resolved, begin IV infusion of antiarrhythmic agent that has aided resolution of VF.

2. Asystole.

- CPR (If rhythm is unclear and possibly VF, defibrillate as for VF).
- Adrenaline 1mg IV or ETT.
- Intubation if not already.
- Consider possible causes and initiate appropriate treatment if identified: Hypoxia, hyperkalaemia, hypokalaemia, preexisting acidosis, drug overdose, hypothermia.
- Consider immediate transcutaneous pacing.
- Adrenaline 1mg IV push; repeat every 3-5 mins.
- Atropine 1 mg IV push or 2mg by ETT; repeat every 3-5 mins up to 3mg IV.
- If no response, consider:
  - High dose adrenaline regimen eg 2-5mg IV push every 3-5 mins or 1mg-3mg-5mg IV push (3mins apart).
  - Consider bicarbonate 50ml of 8.4% IV.
  - Termination of efforts.

Note:

- VF may appear as a ‘flat line’ (asystole) with rhythm recordings from a single placement of the monitor / defibrillator paddles. Therefore, Asystole should be confirmed in 2 leads.
- Sodium bicarbonate is not recommended for routine use early during the resuscitative effort.

3. Electromechanical dissociation (EMD).

- CPR.
- Adrenaline 1 mg IV push; repeat every 3-5 mins.
- Intubate if not already.

- Rule out hypovolaemia, cardiac tamponade, tension pneumothorax, hypoxaemia, acidosis, pulmonary embolism.
- Consider:
  - Presser agents.
  - Calcium.
  - Bicarbonate.
  - Adrenaline 5mg IV.

_ ACUTE HEART FAILURE AND CARDIOGENIC SHOCK

A. Causes

1. **Myocardial Infarction**
2. **Valve and myocardial destruction:**
- Rupture of interventricular septum
- Acute mitral or aortic regurgitation
- Left ventricular aneurysm
3. **Cardiomyopathy**
4. **Myocarditis**
5. **Others:**
- Arrhythmias
- Cardiac tamponade
- Pulmonary embolus
- Aortic dissection

B. Clinical features

1. ***Hypotension*** - systolic arterial pressure < 90mmHg or reduction of >30mmHg of basal level.
2. ***Symptoms & signs of shock*** - cool, diaphoretic skin, cyanosis, dyspnoea, clouded sensorium and decreased urine output.
3. ***Pulmonary oedema.***

- Acutely breathless, orthopnoea, paroxysmal nocturnal dyspnoea, dry cough or coughing with pink frothy sputum.
- Frightened, gasping, pale, cyanosed with cold peripheries, sweating, tachycardia, raised JVP, gallop rhythm, loud P2, pulses alternan, lung crepitation and rhonchi.
- CXR - semiconfluent mottling spreading from hilar, upper lobe diversion, Kerley 'B' lines and pleural effusion.

C. Investigations and Monitoring

1. ***Regular BP or intra-arterial BP monitoring.***
2. ***Urine output (***renal perfusion), ***alertness and conscious level*** (cerebral perfusion) and general wellbeing.
3. ***Assessment of venous pressures:***

- Central venous pressure (only reflects right ventricular filling pressure)
- Pulmonary capillary wedge pressure (PCWP) with Swan-Ganz catheter.

4. ***Echocardiography*.**
5. ***ECG, cardiac enzymes, ABG, CXR, FBC, BUSE and creatinine.***

D Management

1. General measures:

- Patient should be in sitting position (improves pulmonary function and assists in venous pooling). If the patient is hypotensive, they should be placed supine or in trendelenburg position.
- ***Oxygen*** should be given via nasal prong or face mask to maintain PaO2 of >60-70 mmHg or SaO2 of >90%. ***Mechanical ventilation*** is indicated if hypercapnia coexists or if oxygenation is inadequate while on high flow oxygen.
- ***Morphine*** IV 2.5-5mg together with an ***antiemetic*** (metoclopramide 10mg IV or IM) is given and can be repeated as necessary. Morphine reduces anxiety and causes systemic vasodilatation. Naloxone should be available in case of repiratory depression. Morphine should be ***avoided or used with care*** in the presence of hypotension.

2. Fluid therapy:

- Patients presenting with hypotension or other evidence of hypoperfusion should have a trial of volume expansion as long as evidence of clinical or haemodynamic pulmonary congestion is absent.
- Appropriate fluids for volume expansion include ***normal saline*** or ***Ringer's lactate*** solution. There are no compelling advantages to the use of colloid solutions in preference to crystalloid.
  - ***a. If invasive haemodynamic monitoring is not available,*** fluid should be administered in small volumes (100ml) over 5-10 mins intervals with careful reassessment of BP, heart rate, peripheral perfusion, and breath sounds between successive administration. If the blood pressure does not respond to fluid (after about 500-1000ml), a vasopressor should be started.
  - ***b. If invasive haemodynamic monitoring is available,*** volume should be administered until a PCWP of 18 mmHg is attained.

3. Diuretics:

- ***IV loop diuretics*** produce immediate vasodilatation in addition to the more delayed diuretic response. F***rusemide*** 40mg or ***bumetanide*** 1mg can be given and repeated as required at 20 mins intervals if initial therapeutic

response is inadequate. In patients with chronic renal insufficiency, initial doses of 80-160mg of frusemide may be required for the production of significant diuresis. Bumetanide can be given to maximal dose of 10mg.

- Although extremely useful for the treatment of pulmonary congestion, loop diuretics should be ***used with caution*** in patients with significant hypotension.

4. Vasodilators:

a. Venodilators eg. nitroglycerin IVor SL reduces preload, and hence left ventricular end-diastolic pressure.

- ***Contraindicated*** in hypotension (eg. BP <90 mmHg systolic).
- Nitroglycerin is the drug of choice for acute ischaemic pulmonary congestion.
- Nitroglycerin may be administered in sublingual, topical and IV formulations. Sublingual and topical GTN are useful primarily as a bridge until IV therapy can be started.
- Sublingual nitroglycerin 0.3-0.5mg can be given for rapid relief and repeated at 5-min intervals to maximum of 3 tabs. Peak action occurs within 2 min and continues for 15-30mins .
- Topical application can be applied as half to 2 inches of 2%ointment or as sustained release patches 5-15mg. The onset of effects is delayed approximately 30 mins and can persist from 3-6 hours
- IV nitroglycerin should be commenced at 5-10 mcg / min and increased by 5-10 mcg / min every 5-10 mins, if needed to 100-200mcg / min (50mg in 250ml of NS or D5% = 200mcg / ml; 10mcg / ml = 3ml / hr).
- End points for titration with GTN are a 10-15% decline in systolic BP without lowering systolic BP below 100 mmHg, increase in heart rate not exceeding 20bpm, or a decrease of 30% in PCWP.

b. Arteriolar and venodilatation eg. sodium nitroprusside:

- ***Dosage*** - (mix 50mg in 250ml of D5%= 200mcg / ml; 10mcg / min = 3 ml / hr), start at 0.5mcg / kg / min and titrate until the desired effect or blood pressure has been achieved (eg. drop of 10-20 mmHg or SBP of about 100 mmHg). Average effective dose is 3mcg / kg / min (range from 0.5-8 mcg / kg / min).

5. Inotropic agents :

a. Dopamine: beta1-adrenergic action stimulates heart rate and contractility (5-20mcg / kg / min); dopaminergic action causes vasodilation of renal, splanchnic, and coronary vasculatures at low doses (0.5-5mcg / kg / min); alfa-adrenergic action increases mean

arterial pressure, systemic vascular resistance and PCWP by about one-third at high doses (>10-20mcg/kg/min).

- ***Advantages*** - prompt elevation of blood pressure, preservation of renal and mesenteric blood flow.
- ***Disadvantages*** - reflex tachycardia which increases myocardial oxygen consumption, arrhythmogenic potential.
- ***Dosage -*** 5-10mcg/kg/min, rarely exceeding 20mcg/kg/min (mix 800mg in 500ml of NS or D5% = 1600mcg/ml).

b. ***Dobutamine***: acts mainly on beta-1-adrenergic receptors and weakly on beta-2-receptors.

- ***Advantages*** - mild vasodilatation (decreased afterload) & hence reduce PCWP in addition to increased cardiac contractility, no alpha-adrenergic acitvity, little effect on heart rate in lower doses.
- ***Disadvantages*** - arrhythmogenic, positive chronotropic and peripheral vasodilatory effects limit use at higher doses. Can cause hypotension when administered at dosages of 20 mcg/kg/min.
- ***Dosage*** - up to 15-20mcg/kg/min. Desired effects are commonly obtained at dosages from 7.5-15 mcg/kg/min (mix 250mg in 250ml of NS or D5% = 1000mcg/ml).

\# *When there is peripheral hypoperfusion and significant hypotension, dopamine is preferred for its ability to increase mean arterial pressure and restore adequate coronary, cerebral, and renal perfusion.*

\# *In the patient with significant pulmonary congestion and only mild hypotension, dobutamine is preferred.*

\# *Combination of both agents at the modest infusion rate of 7.5ug/kg/min in patients with hypoperfusion, hypotension, and pulmonary congestion minimizes the disadvantages effects of the individual drugs while taking the beneficial effects of both.*

c. ***Noradrenaline/Adrenaline:***

- Noradrenaline is a beta-1 & alpha adrenergic agonist. It increases contractility but also causes peripheral vasoconstriction.
- It is often used when dopamine at a dose of >20mcg/kg/min fails to maintain adequate BP & perfusion.
- Noradrenaline is initiated at an infusion rate of 8-12mcg/min (mix 2mg in 500ml of D5%) & then adjusted upward or downward as indicated by clinical response(usual maintenance dose 2-4mcg/min).
- Adrenaline is often used as alternative (at similar dose) when noradrenaline is not available.

d.. ***Phosphodiesterase-III inhibitors:***

- ***Amrinone*** or ***milrinone*** IV is indicated for cardiogenic shock associated with severe pulmonary congestion, PCWP >24 mmHg if dobutamine and dopamine used alone or in combination are ineffective, and interventional therapy is not appropriate.

- These agent have both inotropic and vasodilating effects and may cause hypotension and is usually less effective than dobutamine.
- Dosages: Amrinone IV bolus 0.75mg/kg over 2-5 mins and then an infusion of 5-10ug/kg/min. An added bolus dose may be given 30 mins later. Milrinone IV over 10 min, 50 ug/kg then IV infusion 375-750 nanograms/kg/min.

6. Others:

- ***Aminophylline*** - loading dose of 250-500mg or 5mg/kg infused over 10 min followed by an infusion at 0.3-0.5mg/kg per hour causes bronchodilatation, vasodilatation and increased cardiac contractility. The dose may need modifying in old or very ill patients. The usage of this agent in the treatment of heart failure, however, should be discussed with the physician.
- ***Mechanical circulatory support*** eg. intraaortic balloon counterpulsation.
- ***Investigation and treatment of the cause or precipitating factors*** eg. anaemia, arrhythmias, hypertension, myocardial infarction, valvular lesion, etc.
- ***Correction of severe acid-base or electrolyte disturbances.***
- ***Dialysis*** - in patients who have renal failure & anuria, dialysis will be required.
- ***Venesection*** - in patients who are fluid overloaded (with Hb >10g/dl), venesection (500cc of blood) may be necessary.

E. Pharmacotherapy by Forrester subset

Forrester Correlative classification of clinical and haemodynamic function after acute myocardial infarction.

Subset	
I	No pulmonary congestion or peripheral hypoperfusion
II	Isolated pulmonary congestion
III	Isolated peripheral hypoperfusion
IV	Both pulmonary congestion and hypoperfusion

A. Subset II: Isolated pulmonary congestion.

- Assuming normal blood pressure and cardiac output, therapy for pulmonary congestion in the setting of ongoing ischaemia should be initiated with GTN.
- Simultaneous adminstration of diuretics would be helpful.
- Severely hypertensive patients may benefit from initial vasodilator therapy with sodium nitroprusside.

B. Subset III: Isolated hypoperfusion.

- Volume replacement should be instituted as explained earlier.
- The majority of patients in this group will be hypotensive, and will require support with inotropes and pressors in addition to volume expansion.
- Both dopamine and dobutamine are capable of augmenting CO in patients with isolated hypoperfusion. When BP is adequate, dobutamine is the preferred agent. However, when MAP is less than 70 mmHg, the pressor effects of dopamine are required to maintain adequate coronary perfusion pressure.

C. Subset IV: Hypoperfusion with pulmonary congestion.

- In the patient with frank hypotension, therapy is best initiated by inotrope therapy with dopamine at 5 mcg/kg/min and titirate to 20mcg/kg/min if required. Noradrenaline or adrenaline should be used in replacement of dopamine if doses of >20mcg/kg/min failed to restored BP and perfusion. Failure to promptly restore adequate arterial pressure while maintaining peripheral perfusion with noradrenaline requires the initiation of mechanical circulatory support.
- Should dopamine succed in elevating MAP to adequate levels, dobutamine may be added to augment cardiac output and allow weaning of dopamine to levels that do not produce unacceptable side effects.
- GTN or nitroprusside might also be added to dopamine to augment SV and reduce filling pressures once systolic BP has been stabilized at >90 mmHg.
- Patients with borderline blood pressure or subclinical hypoperfusion eg. BP of 90-100 mmHg may require support of cardiac output with inotropes. Administration of dobutamine in this setting can augment CO and increase systolic blood pressure to an extent that permits the initiation of vasodilator therapy with GTN. Dopamine is less effective than dobutamine in this setting due to its potential for causing alpha-mediated increases in afterload and increased PCWP. Should MAP fall, dopamine may be added.
- The treatment of pulmonary congestion necessarily takes a back seat to the correction of inadequate perfusion pressure in the majority of patients with cardiogenic shock. Once arterial pressure is stabilized, measures to reduce filling pressure with nitrates and diuretics can be attempted.

_ AORTIC DISSECTION

A. Causes / Predisposing factors

- Atherosclerosis
- Marfan syndrome
- Pregnancy
- Ehlers-Danlos syndrome
- Trauma
- Hypertension
- Advanced age
- Coarctation of the aorta
- Arteritis - Giant cells

B. Clincal features

1. Symptoms:

- ***Severe pain*** at chest, back, abdomen, or the legs, depending upon the origin of the aneurysm (pain may mimick MI except for rapid onset).

2. Signs:

- ***Heart failure*** or ***hypotension***. Exclude pseudohypotension by feeling for peripheral pulse & look for unequal BP in the arms.
- Signs of ischaemia in the :
  - ***Myocardium***.
  - ***Limbs***-pallor, cold and peripheral pulses are absent (a difference of 20mmHg between the systolic arterial pressures of opposite limbs or different limbs indicates arterial obstruction in the limb with lower pressure).
  - ***Brain-*** hemi or quadriplegia.
  - ***Spinal cord***- paraplegia.

- ***Kidneys***- anuria (if both kidneys are involved).
- ***Gut ischaemia***.
- ***Aortic regurgitation.***
- ***Haemopericardium*** or left ***pleural effusion.***

C Investigations

1. **Chest X-ray** - possible findings:
   a. Mediastinal widening.
   b. Change of configuration of the thoracic aorta as compared with old films.
   c. Extension of aortic shadow beyond a calcified aortic wall.
   d. Pleural effusion, most commonly on the left.
   e. Blood around the apex of the lung ('capping').
   f. May be normal.
2. **Echocardiography** (TEE is the better choice)**.**
   - widening of the aorta.
   - double lumen of aorta.
3. **ECG.**
4. **CT scan.**
5. **Aortography** -largely superceded by CT & TEE.

Stanford Classification:

Type A:	Includes all proximal dissections and distal dissections that extend proximally to nvolve the arch and ascending aorta.
Type B:	All other distal dissections without proximal extension.

D Management:

1. **Supportive care:**
- Airway, breathing and circulation should be secured as rapidly as possible.
- Pain control with IV morphine.
- All patients should be admitted to ICU.
- CVP line monitoring would be required.
- Intraarterial BP monitoring.
- Send blood for FBC, BUSE, se creat, ABG & GXM (6-8 units).

2. **Blood pressure control:**
- The blood pressure should be kept in the range of 100-120 mmHg systolic and the heart rate should be kept in the range of 60-80 bpm.
- This is usually accomplished with beta-blockers combined with sodium nitroprusside or other vasodilators. Vasodilators in the absence of beta-blockade theoretically may promote extension of the dissection.
- ***Beta-blockers:***

IV ***propanolol*** 0.5-1mg q5min until the heart rate is between 60-80 bpm or maximal dose of 0.15mg/kg followed later by oral medication.

or

Labetolol either as IV infusion or bolus

[***Infusion*** - Mix 200mg in 200 ml of D5% and run at 1-2mg/min (1-2ml/min). When goal blood pressure is achieved and BP is stable (usually after 50-200mg total amount infused), the infusion can be stopped and oral labetolol be started at a dose of 100-200mg 12hrly.

Bolus - IV 50mg over 1-5 min and can be repeated every 5-10min till maximum dose of 300mg or until desired BP is achieved. Maximum response occur in 5-10 min and may last for up to 6 hours. BP should be checked 5-10 mins after each IV boluses. Oral labetolol can then be started.]

or

IV ***metoprolol*** 5-10mg q6h.

- ***Sodium nitroprusside****:* (mix 50mg in 250ml of D5%= 200mcg/ml; 10mcg/min = 3 ml/hr) start at 0.5mcg/kg/min and titrate until the desirable blood pressure has been achieved. Average effective dose is 3mcg/kg/min (range from 0.5-10mcg/kg/min).
  # If sodium nitroprusside is not available, IV or oral hydralazine, IV GTN or oral nifedepine can be used instead.
- Hypotension may be due to haemorrhage or cardiac tamponade. When hypotension occurs, stop all antihypertensive agents & resuscitate patient with IV fluid.

3. Definitive therapy:

a. Type A: Emergency surgery is indicated.

b. Type B: Medical therapy for stable patients, with surgery reserved for those with any of the following:

- Appearance of aortic regurgitation.
- Pericardial tamponade.
- Leakage of the aneurysm – rupture or impending rupture.
- Occlusion of a major systemic artery – major organ or limb ischaemia.
- Persistence of severe pain or hypertension.
- Progressive enlargement of the aneurysm.
- Saccular aneurysm formation.
- Dissecting aneurysm in Marfan`s syndrome.

4. Chronic therapy:

- In patients who are treated medically or surgically, chronic therapy with a beta-blocker is indicated. Those being treated medically require chronic vasodilator therapy as well. Systolic BP should be aim at 130-140 mmHg.
- Patient will require CT performed once or twice/year.

_ CARDIAC TAMPONADE.

- Cardiac tamponade occurs when a pericardial effusion causes haemodynamically significant cardiac compression.

A. Causes

1. **Infections:**
   Viral eg. coxsackie, influenza
   Bacterial: Pyogenic, TB
   Fungal
2. **Metabolic:**
   Uraemia
   Hypothyroidism
3. **Neoplastic:**
   Ca bronchus
   Lymphomas
4. **Myocardial Infarction**
5. **Radiotherapy**
6. **Autoimmune:**
   Collagen disease: RA, SLE
   Post-pericardiotomy & post infarction
   Serum sickness & drug reactions
   Rheumatic fever
   Idiopathic relapsing pericarditis
7. **Haemopericardium:**
   Cardiac rupture
   Aortic dissection
   Trauma & surgery
   Post cardiac pacing or catheterization.

B. Clinical Features

1. ***May be a preceding history of precordial pain*** followed by increasing dyspnoea.
2. ***Decreased cardiac output:***
   Tachycardia, hypotensive, small pulse pressure, peripheries are poorly perfused, pulsus paradoxus is usually present (May be demonstrated by measuring the systolic arterial pressure in expiration and inspiration. If there is a fall of >10mmHg on inspiration, then pulsus paradoxus is present).
3. ***Increased pressure in the systemic and pulmonary veins:***
   JVP is raised, 'y' descent is rapid, Kussmaul's sign (high JVP which paradoxically rises with inspiration), tachypnoea, orthopnea, wheezing and crepitation.
4. ***Effusion itself:***
   Increased area of dullness around the pericordium, apex beat is impalpable and heart sounds are muffled. Third heart sound may be heard.

* ***Beck's triad***: rising JVP, falling BP, small quiet heart.

C Investigations

1. ***CXR*** - Large globular heart. May be normal in acute tamponade.
2. ***ECG*** - Sinus tachycardia with low voltage complexes. Alternating QRS morphologies (electrical alternans).

3. ***Echocardiography*** - Usually shows large effusion. Echocardiographic features of tamponade include the presence of diastolic collapse of the RA & RV.
4. ***Investigate for causes***.

D. Management

1. **Volume expansion** may be helpful; increasing the preload by maximizing venous pressure with isotonic fluid administration is imperative prior to parenteral inotropic support . **Inotropic agents** may be used as a temporary measure while more definitive treatments are being instituted.

2. **Decompress the heart:**

- ***Indications:*** when the effusion collects rapidly
  when the circulation is embarrassed
  when malignant, TB or purulent effusion is suspected

  # Pericardiocentesis is most likely to be successful and uncomplicated when performed in patients with an anterior clear space of 10mm or more measured by echocardiography.
- ***If trauma is the cause***, treatment is urgent thoracotomy. Pericardiocentesis is to buy time, and should not delay surgery.
- ***If the cause is non trauma:***
  - ***a. If patient is in extremis,*** insert a wide-bore needle in the fourth or fifth left intercostal space 1 to 2 cm medial to the left border of cardiac dullness with the needle directed inward and slightly medially until fluid is obtained.
  - ***b. Otherwise*** the site of choice is the xiphisternal approach. Sit the patient up at $45^{o,}$ insert the needle (14-18 gauge) at left xiphocostal angle advance toward left shoulder at an angle of approximately 30 degrees, aspirating during advancement until fluid is obtained.
    - If effusion is haemorrhagic, place a few millilitres of the fluid in a glass tube, intracardiac blood will clot, haemorrhagic effusion will not. Alternatively, if using echo guidance, inject 5-10ml saline into the needle looking for 'microbubble contrast' in the cavity containing the needle tip.
    - To minimise the chances of entering a cardiac chamber, it is helpful to attach the aspiration needle to the 'V' lead terminal on the ECG cable.
    - Aspirate to dryness and then leave a pericardial drain in situ on free drainage.
    - Send fluid for biochemistry, gram stain, culture, cytology.
    - Romove the drain after 24 hrs or when the drainage stops.

3. **Diuretics, nitrates or any other preload-reducing agents** are ***contraindicated.***

4. **Treat the cause.**

_ INFECTIVE ENDOCARDITIS

A Classifications

1. Clinical classification:
- Native valve endocarditis.
- Prosthetic valve endocarditis.
  a. Early PVE: Occurs within 2 months of replacement.
  b. Late PVE: Occurs after 2 months of replacement.
- Intravenous drug-use-associated endocarditis (IVDU).

2. Acute and subacute classification:
- Divided into acute or subacute forms depending on whether untreated patients could be expected to survive for more than or less than 8 weeks.

3. Classification by aetiological agents.

B Risk factors and common organisms

1. Predisposing factors/Groups at risk of endocarditis:

a. The elderly (>60years).
b. Patients with intrinsic cardiovascular disease:
- Patients with valve prostheses, tissue grafts and other intracardiac foreign material.
- Ventricular septal defect.
- Aortic regurgitation.
- Mitral regurgitation.

- Aortic stenosis.
- Patent ductus arteriosus.
- Coarctation of the aorta.
- Cynotic congenital hearty lesions.
- MVP with regurgitation.
- Hypertrophic obstructive cardiomyopathy.

c. Main-lining drug addicts - right sided valvular endocarditis occurs relatively commonly in this group.

d. Immunosuppressed patients.

2. Organisms causing endocarditis:

a. Native valve endocarditis (NVE):
- Streptococcus viridans
- S. bovis
- Enterococcus fecalis
- Staphylococci
- Gram-negative organisms
- Fungi

b. Right-sided endocarditis (RSE):
- Staphylococci
- Streptococci
- Pseudomonas
- Gram-negative organisms
- Fungi
- Diphtheroids

c. Prosthetic valve endocarditis (PVE-early and late):
- Staphylococci aureus
- Coagulase-negative staphylococci
- Streptococci
- Gram-negative organisms
- Fungi eg. candida
- Diphtheroids

d. Culture-negative endocaridtis:
- HACEK group
- Fungi
- Chlamydia
- Rickettsiae
- Acid fast bacilli

HACEK= Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella

C. Clinical features

1. General:
- Malaise
- Clubbing
- Fever
- Chills

2. Cardiac:
- Murmurs
- Heart failure

3. Skin lesions:
- Osler's nodes

- Splinter haemorrhages
- Janeway lesions
- Petechiae

4. **Eye:**
- Roth spots
- Conjunctival splinter haemorrhages

5. **Neurological:**
- Cerebral emboli
- Mycotic aneurysm

6. **Renal:**
- Haematuria
- Glomerulonephritis

7. **Splenomegaly**

D. Investigations

- Blood cultures (3 times) - 10mls, prior to antibiotic Rx, taken at any time (whether febrile or not).
- FBC, BUSE & ESR.
- Urinalysis (presence of RBC or red cell casts).
- Chest x-ray.
- Serum creatinine.
- Liver functions.
- ECG.
- Echocardiography.

E. Management

1. **General principles:**

- The patient suspected of having endocarditis should have at least 3 separate samples of blood cultured before antibiotic are begun.
- If a stable patient has recently been treated with antibiotics, it is reasonable to obtain several additional cultures in an effort to isolate the causative organism before beginning therapy.
- In acute cases or if risk of death or complication from untreated endocarditis is a significant possibility, empirical therapy should be started as soon as cultures have been taken.
- In subacute infective endocarditis, there should be no rush to starting antibiotics; time should be well spent to obtain an infective proof so as to lend confidence to the choice of antibiotic and the initiation of a very protracted course of treatment.
- If an organism is isolated, antibiotic therapy may need to be modified when sensitivities are known.

2. Empirical Antibiotics:

A. Non-drug addict:

- ***Benzylpenicillin*** 10-20 mega units (2-3mega 4-6 hourly) IV for 4-6 weeks and ***gentamicin*** 1mg/kg IV 8hrly for 2 weeks (after 4 weeks of IV penicillin, replacement with oral penicillin 500mg 6hrly with probenecid 500mg 6hrly may be considered).

or

- If penicillin-allergy: ***vancomycin*** 30mg/kg/day in divided doses eg. 500mg 6hrly (2g/day maximum) for 4 weeks and ***gentamicin*** 1mg/kg (80mg maximum) 8hrly for 2 weeks.

For acute native valve endocarditis, empirical therapy should include antibiotics that are bactericidal against streptococci, staphylococci & enterococci eg. combination of penicillin + cloxacillin + gentamicin can be used.

B. Prosthetic valve endocarditis (or post surgical) or IV drug abusers:

- ***Cloxacillin*** 2g 4hrly IV for 6 weeks and ***gentamicin*** 1mg/kg 8hrly IV for 2 weeks.

or

- If penicillin allergy or if MRSA is suspected: ***vancomycin*** 30mg/kg/day in divided doses IV (maximum 2g/day) for 4-6 weeks and ***gentamicin*** 1mg/kg 8hrly for 1-2 weeks +/- ***rifampicin*** 300mg 12hrly orally for 6 weeks (if MRSA is suspected).

3. Definitive therapy for bacterial endocarditis:

Organism	**Regimen**
Penicillin-susceptible viridans streptococci (MIC _0.1ug/ml)	Penicillin 2-3 mega units IV 4hrly for 4 wks or Cetriaxone 2g IV daily for 4 wks or Penicillin 2-3 mega units IV 4 hrly for 4wks, plus Gentamicin 1mg/kg IV 8hrly for 2 wks or Vancomycin 1g IV 12hrly for 4 wks (for penicillin allergy)
Relatively Penicillin resistant streptococci (0.1ug/ml < MIC _0.5ug/ml)	Penicillin 3 mega units IV 4 hrly for 4wks, plus Gentamicin 1mg/kg IV 8hrly for 2 wks or Vancomycin 1g IV 12hrly for 4 wks (for penicillin allergy; to avoid gentamicin)

Enterocci, Penicillin-resistant Streptococci (MIC >0.5ug/ml)	Penicillin 3-5 mega units IV 4 hrly for 4-6 wks/Ampicillin 2g 4hrly is preferred in enterococci, plus Gentamicin 1mg/kg IV 8hrly for 4-6 wks *(6 wks for enterococci endocarditis; 6 wks for prosthetic valve infection)* or Vancomycin 1g IV 12hrly for 4-6 wks, plus Gentamicin 1mg/kg IV 8hrly for 4-6 wks
Staphylococcus aureus	Cloxacillin 2g 4hrly for 4 wks, plus Gentamicin 1mg/kg IV 8hrly for 2 wks *(omit gentamicin for significant renal insuffiency, cloxacillin for 6 wks in prosthetic valve endocarditis)* or Vancomycin 1g IV 12hrly for 4 wks (*For MRSA use vancomycin + gentamicin +/- rifampicin)*
Coagulase-negative Staphylococci, Prosthetic valve infection	Cloxacillin 2g IV 4hrly for 6 wks, plus Gentamicin 1mg/kg IV 8hrly for 2 wks +/- Rifampicin 300mg bd for 6 wks *(Use vancomycin for 6 wks instead of cloxacillin for MRSA)*
HACEK strains	Ampicillin 2g IV 4hrly for 4 wks, plus Gentamicin 1 mg/kg IV 8 hrly for 4 weks or Ceftriaxone 2g once daily for 4 wks

4. Indications for surgery in infective endocarditis:

Absolute Indications	Refractory heart failure or shock caused by valvular dysfunction.
	Myocardial or perivalvular abscess
	Myocardial spread of infection- complete heart block
	Ineffective medical therapy (persistent pyrexia, persistently positive blood cultures, new murmurs, development of cardiac failure).
	Valve obstruction
	Prosthesis especially unstable or obstructed (especially early infection).
	Fungal endocarditis
	Repeated relapses
	Large vegetations
Relative indications	Myocardial spread of infection - VSD
	Rupture of mitral valve chordae or papillary muscle.
	Periprosthetic leak
	Multiple embolic episodes

5. Monitoring:

- Patient should be ***examined regularly*** for persistent pyrexia, changes in cardiac murmurs, signs of cardiac failure and new embolic phenomena. Persistent fever may be due to drug resistance, concomitant infections or drug allergy.
- ***Echocardiography*** should be repeated (every 1-2 weeks initially) to detect valve dysfunction, development of intracardiac abscesses or vegetations.
- ***ECG*** should be repeated looking for AV block or conduction abnormalities suggesting intracardiac extension of the infection.

- ***Blood culture*** should be repeated if there are symptoms or signs to suggest persistent infection.

6. Endocarditis prophylaxis:

a. Cardiac lesions for which bacterial endocarditis prophylaxis is or is not recommended.

Endocarditis prophylaxis recommended
A. High risk category
Prosthetic cardiac valves, including bioprosthetic and homograft valves Previous bacterial endocarditis, even in the absence of heart disease Complex cyanotic congenital heart disease (eg. single ventricle states, transposition of the great arteries, tetralogy of fallot) Surgically constructed systemic pulmonary shunts or conduits
B. Moderate-risk category
Rheumatic and other acquired valvular dysfunction, even after valvular surgery Hypertrophic cardiomyopathy Mitral valve prolapse with valvular regurgitation and murmur Most other congenital cardiac malformations (other than above and below)
Endocarditis prophylaxis not recommended
Isolated secundum ASD Surgical repair without residua beyond 6 months of secundum ASD, VSD or PDA Previous coronary artery bypass graft surgery Mitral valve prolapse without valvular regurgitation or murmur Physiologic, functional, or innocent heart murmurs Previous Kawasaki disease without valvular dysfunction Cardiac pacemakers and implanted defibrillators Previous rheumatic fever without valvular dysfunction

b. Procedures for which bacterial endocarditis prophylaxis is or is not recommended.

Endocarditis prophylaxis recommended
Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning

Tonsillectomy or adenoidectomy Surgical operations that may interrupt intestinal or respiratory mucosa Rigid bronchoscopy Sclerotherapy for oesophageal varices Esophageal dilatation Gallbladder surgery Cystoscopy Urethral dilatation Urethral catheterization if urinary tract infection is present Urinary tract surgery if urinary tract infection is present Prostatic surgery Incision and drainage of infected tissue Vaginal delivery in the presence of infection
Endocarditis prophylaxis not recommended
Dental procedures not likely to induce gingival bleeding, such as simple adjustment of orthodontic appliances or fillings above the gum line Injection of local intraoral anaesthetic (except intraligamentary injections) Shedding of primary teeth Tympanostomy tube insertion Endotracheal intubation Fiberoptic bronchoscopy with or without biopsy # Cardiac catheterization including balloon angioplasty Transeosophageal echocardiography # Implanted cardiac pacemakers, implanted defibrillators, and coronary stents Endoscopy with or without gastrointestinal biopsy # Vaginal hysterectomy # Cesarean section Vaginal delivery # In the absence of infection: urethral catheterization , D & C, therapeutic abortion, sterilisation procedures, or insertion or removal of IUCD Incision or biopsy of surgically scrubbed skin Circumcision

 # Prophylaxis is optional for high-risk patients

c. Prophylactic Regimens for Dental, Oral, Respiratory Tract, or Esophageal Procedures ; AHA recommendations 1997

Situation	**Regimen**
Standard general prophylaxis	Amoxicillin 2 g 1 h orally before procedure
Unable to take oral medications	Ampicillin 2 g IM or IV within 30 min before procedure
Allergic to penicillin	Clindamycin 600mg 1 hr before procedure or Cephalexin or cefadroxil 2 g 1 hr before procedure or Azithromycin or clarithromycin 500mg 1 hr before procedure
Allergic to penicillin and unable to take oral medications	Clindamycin 600mg IV within 30 min before procedure or Cefazolin 1 g IM or IV within 30 min before procedure

d. Prophylatic Regimens for Genitourinary, Gastrointestinal (Excluding oesophageal) procedures; AHA recommendations 1997

Situation	**Regimen**
High risk patients	Ampicillin 2 g IM or IV plus gentamicin 1.5mg/kg (not to exceed 120mg) within 30 min of starting the procedure; 6 hrs later, ampicillin 1 g IM/IV or amoxicillin 1 g PO

High-risk patients allergic to ampicillin / amoxicillin	Vancomycin 1 g IV over 1-2 hr plus gentamicin 1.5mg / kg IV or IM (not to exceed 120mg); complete injection / infusion within 30 min of starting the procedure
Moderate-risk patients	Amoxicillin 2 g PO 1 h before procedure or ampicillin 2 g IM / IV within 30 min of starting the procedure
Moderate-risk patients allergic to ampicillin / amoxicillin	Vancomycin 1 g IV over 1-2 h; complete infusion wihin 30 min of starting the procedure

2. PULMONARY DISEASE

ACUTE EXERCEBATION OF BRONCHIAL ASTHMA

- Due to the potentially life-threatening nature of severe exacerbation of asthma, treatment should be started as soon as the exacerbation is recognized and a quick assessment is made. More detailed assessment, including laboratory studies, should be delayed until after initial therapy has been completed.

A. Assessment

History .
Clinical Examination.
Peak Flow Measurement (PEFR).
Arterial Blood Gases - in patient who has any of the severe or life threatening features.

1. Features of severe asthma:
- Cannot complete sentence in one breath.
- Respiration (per minute): 25 or more.
- Pulse (per minute): 120 or more.
- PEFR usually 33-50 % of predicted (refer to nomogram) or best.

2. Features of life threatening asthma:
- Silent chest, cyanosis, feeble respiratory effort.
- Bradycardia.
- Hypotension.
- Exhaustion, confusion or coma.
- PEFR usually less than 33 % of predicted or best (or a single reading of <150L / min or patients who are not able to blow).
- ABG markers of very severe, life threatening atttack include:
  - a normal (5-6kPa, or 36-45mmHg) or high PaCO2
  - severe hypoxaemia (PaO2 <8kPa or 60mmHg) irrespective of treatment with oxygen
  - a low PH.

B. Mangement of Acute Asthma in Accident and Emergency Department

1. Mild attack of asthma ***(PEFR more than 75 %, no features of severe / life threatening symptoms):***
- Give usual ***inhaled bronchodilator*** or ***nebulised with beta2 agonist.***
- Observe for 60 minutes .
- If stable and PEFR remains more than 75 %, allow home with adequate supply of medication (at least 1000mcg inhaled beclomethasone or equavalent per day). Ensure that inhaler technique is correct and a follow up review is arranged.

- Advise patient to return immediately if asthma worsens.
- Patients should be considered for admission if social situations such as staying alone, lack of transport for emergency visit to hospital etc are present. Consider admission also for patients with history of brittle asthma or previous attacks requiring mechanincal ventilation.

2. Moderate attack of asthma ***(PEFR 50-75%, no symptoms of severe / life threatening asthma):***

- Immediately give ***nebulised salbutamol*** 5 mg or ***terbutaline*** 10 mg with **OXYGEN** as driving gas and oral prednisolone 30-60mg daily. Alternatively, beta2 agonist may be given by multiple actuations of a pressurised aerosol inhaler into a large spacer device (2-5mg ie 20-50 puffs, five puffs at a time).
- Reassess in 30 minutes:
  a) If condition remains unchanged, repeat nebulised beta agonist .
  b) If condition worsens or PEFR less than 50 %, arrange admission.
- Reassess in 30 minutes:
  a) If PEFR is more than 75% and condition stable, patient can be allowed home with prednisolone 30-60mg daily for 5-10 days, regular inhaled corticosteroids (at least 1000mcg inhaled beclomethasone or equivalent per day) and beta agonist as necessary. Advise patient to return if asthma worsens. Arrange for early review in clinic.
  b) If condition worsens or PEFR less than 75%, arrange admission.

3. Severe or life threatening attack of asthma ***(PEFR <50 % and /or features of severe or life threatening asthma):***

- Immediately give ***nebulised salbutamol*** 5 mg or ***terbutaline*** 10 mg with **OXYGEN** as driving gas. Add ***Ipratropium*** 0.5 mg to nebulised beta agonist.
- Give oxygen 40-60 %.
- ***Intravenous hydrocortisone*** 200 mg or ***oral prednisolone*** 30-60mg. There are no clinical effects for the first 4-6 hours. Therefore it is important to begin steroids early and to use intensive bronchodilator treatment while waiting for them to take effect.
- If life threatening features are present, give ***intravenous aminophylline*** 250 mg over 20 minutes (do not give bolus aminophylline to patients already taking oral theophyllines) or ***salbutamol*** 250 mcg over 10 minutes or ***terbutaline*** 250 mcg over 10 minutes.
- ***Chest radiography*** to exclude pneumothorax or lung collapse.
- ***Arrange admission,*** accompanied by doctor or nurse.
- ***Antibiotic*** are usually not indicated.
- ***Anxiolytic and hypnotic drugs*** SHOULD NOT BE GIVEN because of their respiratory depressant effects.

C. Subsequent Management in the Ward or ICU

1. If patient is improving, continue:

- Oxygen at 40%.

- ***IV hydrocortisone*** 200mg 6 hourly or ***prednisolone*** 30-60mg daily. In patients who are given IV hydrocortisone, after 24 hrs, if there has been a substantial improvement, oral prednisolone at 30-60mg/day (or 0.5-1mg /kg) should be substituted. Oral prednosolone should be continued for 7-14 days. The dose may then be tailed off slowly or, after short courses (eg. <7days), stopped abruptly.
- ***Nebulized beta2 agonist*** regularly eg. 2-4 hourly; this can subsequently be reduced when patients improve and changed to metered dose inhaler.

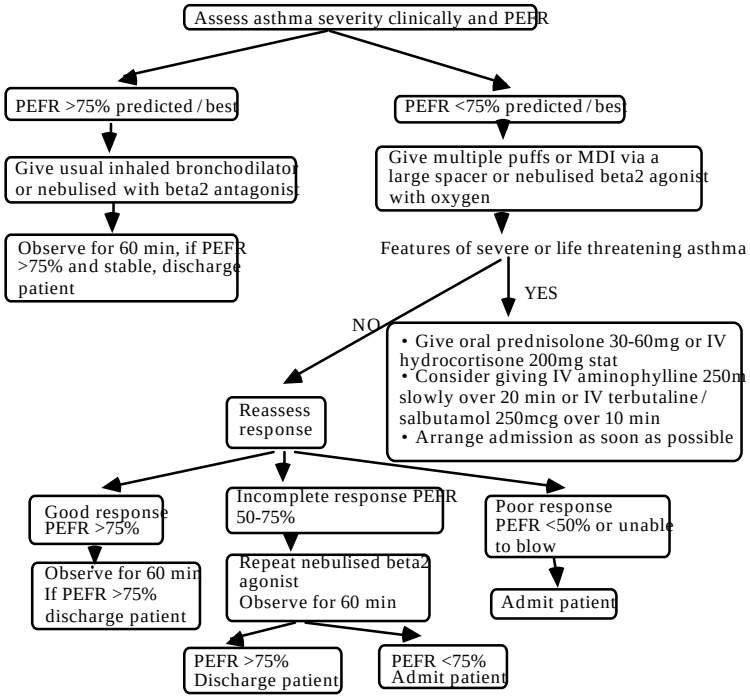
2. If patient is not improving after 15-30 mins:
- Continue ***oxygen and steroids.***
- Give ***nebulised beta agonist*** more frequently, up to every 15-30 mins.
- Add ***ipratropium*** 0.5mg to nebuliser and repeat 6 hourly until patient is improving.
- Consider ***IV aminophylline*** infusion (mix 250mg or 500mg in 500ml of NS or D5%) at a rate of ***0.5-0.9mg/kg/hour; 0.5mg/kg/hour for non smoker, 0.8-0.9mg/kg/hour for smoker, 0.3mg/kg for older patient, 0.1-0.3mg/kg/hour for patient with heart failure, cirrhosis or on cimetidine, ciprofloxacin or erythromycin;*** monitor blood levels if aminophylline infusion is continued for more than 24 hours (therapeutic levels 10-20mcg/ml or 55-110umol/l).
- ***Salbutamol (or terbutaline) infusion*** as an alternative to aminophylline, salbutamol infusion (mix 5mg of salbutamol and 2.5mg of terbutaline in 500ml of NS or D5%) can be given at 3-20mcg/min (Terbutaline 1.5-5mcg/min) after an initial IV bolus dose of 250mcg over 10 mins. They can also be given as SC/IM at a dose of 500mcg repeated every 4 hourly as necessary.
- Intubation and mechanical ventilation are required in patients with ***severe respiratory distress, worsening hypoxaemia, mental status changes, obvious exhaustion, or CO2 retention.***

3. Monitoring the effects of treatment:
- Repeat measurement of PEFR 15-30 mins after starting treatment.
- Maintain arterial oxygen saturation above 92%.
- Repeat arterial blood gas measurement if initial results are abnormal or if patient deteriorates.
- Chart PEFR before and 15 mins after giving nebulised or inhaled beta2 agonist at least 4 times daily throughout the hospital stay.
- Monitor serum electrolytes (hypokalaemia is a recognised complication of treatment with beta2 agonist and corticosteroids).

4. Before discharge, the patient should be:
- Started on inhaled steroids for at least 48 hours in addition to a short course of oral prednisolone and bronchodilators.
- Stable on the medication he is going to take outside the hospital for at least 24 hours.
- Having PEFR of >75% of predicted or best value and PEF diurnal variability of < 20%.
- Taught and checked on the correct inhaler technique and if necessary, alternative inhaler devices should be prescribed.

- Educated on the discharge medication, home peak flow monitoring and self management plan, and the importance of regular follow-up.

D. Summary of Emergency Room Management of Acute Asthma



Normogram:

ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

- Acute exacerbation of COPD presents as a worsening of the previous stable situation. Important symptoms include:
  - Increased sputum purulence, increased sputum volume, increased dyspnoea, increased wheeze, chest tightness and fluid retention.
- Most instance are precipitated by respiratory tract infections, both upper and lower.

- Many patients can be managed at home but some require inpatient support and the decision whether or not to admit is complicated (see table below).

Deciding whether to treat an acute exacerbation at home or in hospital

	Treat at home	**Treat in hospital**
Ability to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor-deteriorating
Level of activity	Good	Poor / confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Living alone / not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Changes on CXR	No	Present
Arterial PH level	≥7.35	<7.35
Arterial PaO2	≥7kPa (52mmHg)	<7kPa(52mmHg)

The more of the referral indicators that are present, the likely the need for admission to hospital
LTOT-Long term oxygen therapy.

A. Management of an Acute Exacerbation as Outpatient

1. **Add or increase bronchodilators** ***ie. beta2 agonist and ipratropium bromide*** (consider if inhaler device and technique are appropriate).

2. **Antibiotics** if two or more of the three features described below are present:
   - ***i. Increased breathlessness.***
   - ***ii. Increased sputum volume.***
   - ***iii. Development of purulent sputum.***

- For choices of antibiotics, please refer later section.

3. **Oral corticosteroids** in some cases if:
   - ***the patient is already on oral corticosteroids.***
   - ***there is previously documented response to oral corticosteroids.***
   - ***the airflow obstruction fails to respond to an increase in bronchodilator dosage.***
   - ***this is the first presentation of airway obstruction.***

- Oral corticosteroids eg prednisolone is given in a dose of 30mg per day for one week.

4. The response to treatment should be reassessed early as outpatient and consideration should be made for admission if the patient fails to response to treatment.

B. Management of an Acute Exacerbation of COPD in Hospital

1. Investigations within 24 hours of admission should include FBC, BUSE, ECG, culture of sputum (if sputum is purulent), blood culture (if pneumonia is suspected), CXR, ABG, and serial peak flow chart started (in patients who could still use peak flow meter) as soon as possible.

2. Oxygen:

- Should be administered to maintain a PaO2 of 55-60mm Hg (88-90% saturation) without a fall in pH (secondary to a rise in PaCO2). It can be given by nasal canula 1-2L/min or 24-28% oxygen by mask. Higher levels of O2 may result in PaCO2 elevation, with consequent depression of mental status, hypoventilation, and further impairment of gas exchange.
- Check ***ABG*** within 60 mins of starting O2 or change of O2 concentration. If PaO2 improves with no or minimal deterioration in pH, then the inspiratory concentration can be increased and the blood gas tensions rechecked.
- If the PH falls or PCO2 rises, consider alternative strategies eg IPPV, NIPPV, if the chance of weaning off is good, ie NOT endstage COPD.

3. Nebulized bronchodilators:

- ***ß2-adrenergic agonists*** (salbutamol 2.5-5mg or terbutaline 5-10mg) with or without ***anticholinergic agents*** (ipratropium bromide 0.25-0.5mg) should be given on arrival and at 4-6 hourly internals thereafter but may be used more frequently if required.
- Nebulizer should be driven by compressed air rather than O2.
- Oxygen can continue to be given by nasal prongs at 1-2L/min during nebulisation in order to prevent the fall in oxygen saturation.

4. Aminophylline:

- Administration should be considered in patients who respond poorly to nebulized bronchodilators.
- ***Bolus dose:*** Aminophylline intravenous 250 mg over 20 minutes (do not give bolus aminophylline to patients already taking oral theophyllines) followed by infusion (mix 250mg or 500mg in 500ml of NS or D5%) at a rate of ***0.5-0.9mg/kg/hour; 0.5mg/kg/hour for non smoker, 0.8-0.9mg/kg/hour for smoker, 0.3mg/kg for older patient, 0.1-0.3mg/kg/hour for patient with heart failure, cirrhosis or on cimetidine, ciprofloxacin or erythromycin.***
- Monitor blood levels if aminophylline infusion is continued for more than 24 hours (therapeutic levels 10-20mcg/ml or 55-110umol/l).

5. Corticosteroids:

- IV or oral corticosteroids may be useful if:
  - ***the patient is already on oral corticosteroids.***

- *there is previously documented response to oral corticosteroids.*
- *the airflow obstruction fails to respond to an increase in bronchodilators dosage.*
- *this is the first presentation of airways obstruction.*

- Corticosteroids can be given as prednisolone 30mg/day or IV 200mg hydrocortisone if the oral route is not possible for 7-14 days.
- A 'trial' of oral corticosteroids (usually 30-40mg/day for 2-3 weeks) can be done, if not already, to determine the need for long term inhaled corticosteroids. As a rule of thumb, patients who show a 20%improvement in PEFR or FEV1 (mean of last 3 days readings) over baseline (mean of first 3 days readings) in a trial can be considered for maintenance inhaled corticosteroid treatment.

6. Antibiotics :

- Antibiotics should be given if two or more of the three features described below are present:
  i. Increased breathlessness.
  ii. Increased sputum volume.
  iii. Development of purulent sputum.
- All patients with acute on chronic respiratory failure (PH<7.35) should also receive antibiotics.
- Common antibiotics will usually be adequate but the antibiotics used should have activities against Strep pneumoniae, H influenzae & Moraxella catarrhalis; ***amoxycillin or doxycycline*** are first choice unless used with poor response prior to admission.
- For more severe exacerbations, or if there is lack of response to the above agents, several second line alternatives can be considered eg. ***2nd or 3rd generation cephalosporin, amoxicllin-clavulanate, ciprofloxacin or the newer macrolides (eg. clarithromycin or azithromycin).***

7. Chest physiotherapy - may be beneficial to improve clearance of secretions.

8. Hydration and diuretics - COPD patients are sensitive to changes in fluid status, and intravenous rehydration is almost always necessary unless there is clinically evident of cor pulmonale with peripheral oedema when fluid replacement ought to be under taken more cautiously.

9. Mechanical ventilation may be considered in patients with acute ventilatory failure. Mechanical ventilation is withheld in endstage disease, when permanent ventilator dependence is likely. In general, the following factors can be used to guide the decision for ventilation:

a. Factors to encourage use of IPPV:

- A demonstrable remedial reason for current decline - for example, radiographic evidence of pneumonia or drug overdosage.
- The first episode of respiratory failure.
- An acceptable quality of life or habitual level of activity prior to exacerbation.

b. Factors likely to discourage use of IPPV:

- Previously documented severe COPD that has been fully assessed and found to be unresponsive to relevant therapy.
- A poor quality of life - for example, being housebound, in spite of maximal appropriate therapy.
- Severe co-morbidities - for example bronchogenic neoplasia.

10. Monitoring and management as the patient recovers:

- ***FEV1*** should be measured prior to discharge in centres where spirometry is available.
- ***Nebulized bronchodilators*** should be continued until the patient is improving clinically. Bronchodilators can then be given by metered dose aerosol or dry powder inhalers, ideally at least 24-48 hours before discharge.
- If ***corticosteroids*** have been used they can usually be stopped abruptly after seven days unless there are positive reasons for long term usage.
- ***Before discharge***, the following should be done:
  - A review of all medications.
  - Check inhaler technique.
  - Ensuring that the patient knows how and when to take his/her medication.

PNEUMONIA

Classification of pneumonia

1. Community acquired pneumonia.
   (a) Primary pneumonia in healthy adult.
   (b) Secondary pneumonia in patient with debility eg COPD.
2. Hospital acquired (Nosocomial) pneumonia.
3. Aspiration pneumonia.
4. Pneumonia in the immunocompromised host.

Important causes of community acquired pneumonia

a. Healthy adult.

1. Streptococcus pneumoniae.
2. Haemophilus influenzae.
3. Mycoplasma pneumoniae.*
4. Respiratory viruses.*
5. Legionella pneumophila.*
6. Chlamydia psittaci.*
7. Coxiella burnetii*

* *Present as Atypical pneumonia.*

b. Patient with debility.

1. Streptococcus pneumoniae.
2. Respiratory viruses.
3. Haemophilus influenzae.
4. Moraxella catarrhalis.
5. Klebsiella pneumoniae.
6. Enteric gram negatives.
7. Staph aureus.
8. Mycobacteria.

Important causes of hospital acquired pneumonia

1. Gram negative bacteria (esp. Klebsiella sp & Pseudomonas aeruginosa, Enterobacter sp, E coli, Proteus, Serratia).
2. Staphylococcus aureus.
3. Anaerobes.
4. Streptococcus pneumoniae.
5. H. influenza.

Important causes of pneumonia in the immunocompromised host

1. Pneumocystis carinii.
2. Mycobacteria.
3. Viruses (eg.Cytomegalovirus, Herpes simplex).
4. Fungi (Candida, Aspergillus, Cryptococcus).
5. Strongyloides stercoralis.
6. Enteric gram negatives.
7. Enteric anaerobes.

A Clinical Features

- *Traditionally divided into 2 clinical patterns:*

a. ***"Typical" pneumonia*** - characterized by a sudden onset of illness with high fever, sweats, rigors, pleuritic chest pain, cough, sputum production, haemoptysis, dyspnoea, tachypnoea, tachycardia, pleural rub, rhonchi and signs of consolidation and a 'toxic' appearance. Chest X-ray shows a lobar or lobular opacity. White cell count is usually markedly elevated.

b. ***"Atypical" pneumonia***- characterized by a gradual onset of non-productive cough, dyspnoea, constitutional symptoms and low grade fever. Clinical findings are often minimal. White cell count is often not elevated. Chest X-ray characteristically show a diffuse bilateral pulmonary infiltrate which appears worse than accounted for by the clinical signs.

B. Investigations

1. ***General:*** FBC, BUSE, CXR, LFT, se creatinine, ABG, cold agglutinins (if mycoplasma suspected), etc.
2. ***Microbiology diagnosis:***

- Sputum culture and microscopy.
- Blood culture.
- Acid fast bacilli.
- Pleural aspiration for analysis and cultures if effusion is present.
- Bronchoscopy should be considered in solitary lung abscess.
- Serology (or serum antibody titres) for mycoplasma, chlamydia, legionella or viruses when atypical pneumonia is suspected. A rising titre over a 2 week interval may provide a retrospective diagnosis. Persistently high antibody titre can also be suggestive.
- Immunofluorescence or Giemsa stain for pneumocystis carinii from induced sputum or bronchial lavage specimens.

- If the patient is very ill or has not responded to conventional treatment, the correctness of the diagnosis or the aetiological agent and the possibility of an occult underlying bronchogenic malignancy must be suspected. In such a case the following tests may be done:
  i) Bronchoalveolar lavage.
  ii) Percutaneous lung aspiration.
  iii) Lung biopsy (transbronchial / open lung biopsy).

Indications for hospitalization for community acquired pneumonia

- Age >60.
- Coexisting illnesses eg alcoholism, DM, COPD, LVF.
- Alteration in vital signs eg hypotension.
- Leukopenia or marked leukocytosis.
- Any evidence of respiratory failure.
- Alteration in mental status eg. confusion
- CXR shows multilobar involvement
- Urea > 7 mmol / L
- Septic appearance.
- Absence of supportive care at home.

C. Management

1. **Antibiotics:**

- Empirical antibiotic therapy is started before the actual microbiological diagnosis is established. Such antibiotic therapy is based primarily on host status, clinical pattern (eg.typical or atypical), CXR appearance, gram stain findings, etc.
- Antibiotics can be given orally unless there is vomiting, fever >38^{O}C or significant hypoxia (PaO2<8kPa, or <60mmHg) when they should be given intravenously.

a. Community acquired pneumonia:

(i) Mild (healthy adult, age≤60):

Erythromycin stearate 500mg orally 6hrly (or erythromycin ethylsuccinate 800mg bd) for 7-14 days

or

Doxycycline 100mg for 7-14 days

or

Second generation cephalosporin (eg. cefuroxime axetil 500mg bd) for 7-14 days

or

Beta-lactam - beta-lactamase inhibitors (eg. augmentin 375mg tds) for 7-14 days

or

Azithromycin 500mg od for 3 days

or

Clarithromycin 250mg bd for 7-14 days

(ii) Moderate to severe or with coexisting conditions # or age>60 yr:

Second generation cephalosporin (eg. cefuroxime axetil 500mg bd or IV cefuroxime 750-1500mg 8hrly)

or

Third generation cephalosporin (eg. IV ceftriaxone 1-2g 12-24 hrly, up to 4g/d)

or

A beta-lactam-beta-lactamase inhibitor (eg. augmentin PO 375-750mg tds or IV 1.2g 8hrly)

with or without

Erythromicin or another macrolide

 # Comorbid illnesses include COPD, DM, renal insufficiency, CCF, hospitalization within past year, post-splenectomy state, chronic alcohol abuse, malnutrition, altered mental status & suspected aspiration.

(iii) Severely ill patient:

(defined as respiratory rate >30/min, PaO2/FIO2 ratio <250mmHg, requirement for mechanical ventilation, CXR showing bilateral or multiple lobar involvement, SBP < 90mmHg or DBP <60mmHg, requirement for vasopressors >4 hrs or renal failure).

Erythromycin 500-1000mg (50mg/kg/day) IV 6 hrly 10-14 days

Plus

Third-generation cephalosporin with antipseudomonal activity (eg. IV ceftazidime 2g 8hrly, cefoperazone 2g 12hrly etc)

or

Other antipseudomonal agent eg. imipenem (250-500mg IV every 6-8 hrly) or ciprofloxacin (IV 200-400mg 12hrly) for 10-14 days if pseudomonas is suspected

Plus

Aminoglycosides eg. Gentamicin 1-1.5mg/kg IV 8hrly for 7-10 days

+/-

IV cloxacillin 500-1000mg 6 hourly if staphylococcus pneumonia is probable ie *a) if there is recent influenza b) cavitation on CXR c) Gram-stain of sputum shows cluster of gram positive cocci.*

(iv) Atypical pneumonias:

Erythromycin stearate 500-1000mg orally 6hrly (or erythromycin ethysuccinate 800mg bd)

or

Azithromycin 500mg od (total dose of 1.5g)

or

Clarithromycin 250mg bd

or

Doxycycline 100mg orally 12hrly (if patient cannot tolerate macrolide).

#Legionella, mycoplasma and chlamydia pneumonia should be treated for a total duration of 14-21 days.

b. Hospital acquired pneumonia *(Defined as pneumonia occuring 48 hrs or longer after admission and not incubating at the time of hospitalization)*:

(i) Mild to moderate outside ICU:

Second or non-antipseudomonal third generation cephalosporin or beta-lactam-beta lactamase inhibitors

plus

Aminoglycosides eg. gentamicin for 10-14 days (or quinolones eg IV ciprofloxacin 200mg 12hrly)

(ii) Severe or ICU or ventilator associated:

Antipseudomonal third generation cephalosporin or antipseudomonal penicillin (Piperacillin 3-4g 6 hrly) or imipenem-cilastatin

plus

Gentamicin or another aminoglycoside (or Quinolones)

+/-

Cloxacillin 1g IV 6hrly or vancomycin for 10-14 days

+/-

Erythromycin if Legionella pneumonia is suspected.

c. Immunocompromised patients:

Treat as in severe or ICU or ventilator associated pneumonia

plus

Consider cotrimoxazole / pentamidine, anti-TB, amphotericin, metronidazole, depending on clinical picture.

Treatment regime for Pneumocystis carinii pneumonia

- TMP/SMX 15mg TMP/kg daily divided QID PO or IV
  or
  Pentamidine 4mg/kg OD IV
  or
  Dapsone 100mg OD (check G6PD) plus TMP 15-20mg/kg daily divided QID
  or
  Clindamycin 450mg QID plus primaquine 30mg OD
- Treatment should be continued for 14-21 days.
- Prednisolone should be added to the initial treatment in patients with moderate to severe respiratory distress defined by an arterial oxygen pressure of <75mmHg on room air. Even patients with milder PCP are likely to benefit - prednisolone should be given at a dose of 40mg bd for 1 week, followed by 40mg od for 1 week and then followed by 20mg daily for 1 week.

d. Lung abscess:

Benzylpenicillin 1-2 mega U IV 6 hrly (or Penicillin V 0.5-1g 6hrly may be used after improvement with IV penicillin) for 4-6 weeks
plus
Gentamicin 1-1.5mg/kg IV or another aminoglycoside for 14 days
plus
Metronidazole 500mg IV 8 hrly or PO 400mg tds for 14 days

Note:
**Prolonged treatment* of up to 4 months may be necessary in some cases in order to achieve cure without relapse.
**Substitute cloxacillin for benzylpenicillin* where staphylococcus aureus is a likely aetiological agent.
**Surgical resection or percutaneous drainage* of a lung abscess is only rarely required for a nonresolving abscess with persistent fevers and leukocytosis despite appropriate medical therapy, the development of a bronchopleural fistula, empyema, persistent haemoptysis, evidence of an enlarging cavity or mechanical ventilation dependence.

***Once organism's sensitivities have been determined, therapy should be revised to the most appropriate antibiotics.***

***In case of treatment failure, to consider:***
- ***Incorrect diagnosis, eg. pulmonary infarct***
- ***Resistant organisms, eg. ampicillin-resistant H. influenzae***
- ***Resistant infection, eg. tuberculosis, an immunocompromised host***
- ***Development of complications, eg. empyema, lung abscess***
- ***Preexisting underlying lung disease, eg. lung tumour, bronchiectasis***

2. **Bed rest** with patient sitting up.

3. **Oxygen** - In the absence of hypoxia, look at the PaCO2: a low PaCO2 indicates the need for oxygen in a patient working hard to maintain a normal PaO2.

4. **Fluids** - Dehydration should be corrected. Patients with severe pneumonia should receive IV fluids to meet the increased fluid demands (a minimum of 3 litres is usually indicated) with a daily check of urea & electrolytes.

5. **Physiotherapy** - chest physiotherapy is an important adjunct to clearing secretions.

6. **Inotropic drugs and mechanical ventilation** may be required.

D Footnotes

Characteristics and treatment of selected pneumonias

Organism	Clinical setting	CXR findings & gram-stain smears of sputum	Antimicrobial therapy
Streptococcus pneumoniae (pneumococcus)	Chronic cardiopulmonary disease; follows upper resp tract infection	Lobar consolidation Gram positive diplococci	P: Penicillin G or V A: Erythromicin, cephalosporin
Haemophilus influenzae	Chronic cardiopulmonary disease; follows URTI	Lobar consolidation Pleomorphic gram-negative coccobacilli	P: Cefotaxime or Ceftriaxone A: Cefuroxime
Staphylococcus aureus	Influenza epidemics; nosocomial	Patchy infiltrates Gram pos cocci in clumps	P: Penicillinase-resistant penicillin eg Cloxacillin A: Cephalosporin, Vancomycin MRSA: Vancomycin
Klebsiella pneumoniae	Alcohol abuse, DM, nosocomial	Lobar consolidation Gram-neg encapsulated rods	P: Cefotaxime, Ceftriaxone, or Ceftazidime (+ aminoglycoside if severe infection). A: Ampicillin-sulbactam, imipenem, amoxycillin-clavulanic acid
Escherichia coli	Nosocomial; rarely community- acquired	Patchy infiltrates, pleural effusion Gram-neg rod	Same as for Klebsiella
Pseudomonas aeruginosa	Nosocomial; cystic fibrosis	Patchy infiltrate, cavitation Gram-neg rods	P: A broad spectrum beta-lactam (antipseudomonal penicillin, 3rd G anti pseudomonal ceph, ciprofloxacin, imipenem) plus an aminoglycoside
Anaerobes	Aspiration, periodontitis	Patchy infiltrates in dependent lung zones Mixed flora	P: Penicillin G. A: Clindamycin, chloramphenicol, metronidazole, ampicillin-sulbactam, amoxycillin-clavulanic acid, imipenem

Mycoplasma pneumoniae	Young adults	Extensive patchy infiltrates PMNs and monocytes; no pathogens	P: Erythromycin A: Tetracycline, doxycycline, clarithromycin or azithromycin
Legionella sp	Exposure to contaminated construction site, water source, air conditioner; community-acquired or nosocomial	Patchy or lobar consolidation Few PMNs; no bacteria	P: Erythromycin A: TMP-SMX, azithromycin, clarithromycin or ciprofloxacin
Chlamydia pneumoniae	Mild pneumonia in teenagers and young adults	Subsegmental infiltrate. Non-specific	P: Tetracycline A: Erythromicin, clarithromycin or azithromycin
Moraxella catarrhalis	Preexisting lung disease; elderly; corticosteroid or immunosuppressive therapy	Patchy infiltrates; occasionally lobar consolidation	P: TMP-SMX A: Amoxicillin-clavulanic acid, erythromyin, tetracycline, cefuroxime or cefotaxime
Pneumocystis carinii	AIDS, immunosuppresion or cytotoxic therapy, cancer	Difuse interstitial and alveolar infiltrates; apical or upper lobe infiltrates in patients on aerosolized pentamidine Not helpful in diagnosis	P: TMP-SMX, pentamidine IV plus prednisolone A: Dapsone & trimethoprim, clindamycin and primaquine

P: Preferred A: Alternative

ACUTE RESPIRATORY DISTRESS SYNDROME.

- Formerly called adult respiratory distress syndrome.
- The term is used to describe a pulmonary condition usually follows a major systemic insult, characterised by progressive hypoxaemia, chest X-ray infiltrates and reduced lung compliance in the presence of a normal left atrial pressure. It is due to diffuse damage to the pulmonary capillary endothelium, which results in increased leakage of plasma and red blood cells into the interstitial space causing interstitial oedema.

A. Causes

- Septicaemia, major trauma, haemorrhagic shock, DIVC, massive transfusion, major pulmonary infection, aspiration, oxygen toxicity, irritant gas inhalation, fat or amniotic fluid embolism, drug overdose, metabolic disorders, intracerebral bleed or oedema, pancreatitis, etc.

B. Diagnosis

1. The syndrome usually develops insidiously ***12-72*** hrs following the precipitating event.
2. ***Usual features*** are dyspnoea, tachypnoea (>20/min), laboured breathing, cyanosis and fine crepitations in both lung fields.
3. ***ABG*** reveals severe hypoxaemia (refractory to treatment with supplemental oxygen indicating shunting), ratio of partial pressure of oxygen in arterial blood (PaO2) to fractional concentration of inspired oxygen (FIO2) <200 mmHg. ***CXR*** shows widespread, diffuse opacification (cardiomegaly or pulmonary vascular redistribution are absent), normal left heart pressures (PCWP < 18 mmHg).
4. ***Chronic pulmonary disease*** and ***left heart abnormalities*** need to be excluded.

C. Management

1. **Oxygenation** - The mainstay of treatment is mechanical ventilatory support. Continuous mechanical ventilation (CMV) using intermittent positive pressure ventilation (IPPV) may be used. If oxygenation cannot be maintained at an adequate level with FiO2 of 60%, then ***positive end expiratory pressure*** (PEEP) should be used at a range of 5-15cm H2O (0.5-1.5kPa). However, it may decrease cardiac output and increase risk of barotrauma.

2. **Fluid management** - Fluid administration must be carefully controlled to allow improvement of systemic and pulmonary perfusion without aggravating the pulmonary oedema. CVP measurement is not adequate. A ***Swan-Ganz catheter*** measuring pulmonary capillary wedge pressure (PCWP) may be needed and PCWP should be kept at 8-12 cm H2O. Other parameters like blood pressure, peripheral perfusion, and urine output should also be assessed. Fluid can be given as colloid, crystalloid or salt free albumin. IV frusemide should be used in patient with fluid overload.

3. **Cardiac Support** - Optimal preload is achieved with fluid administration according to the PCWP. Inotropic agents such as ***dopamine*** (low dose 2-5mcg/kg/min) or ***dobutamine*** (2.5-10mcg/kg/min) are necessary in some patients if cardiac output cannot be maintained and urine output is poor despite adequate hydration.

4. **Specific therapy** for ARDS is not yet available. Early corticosteroid therapy does not prevent the development of ARDS or alter its outcome. Corticosteroids during the fibroproliferative phase of ARDS may hasten recovery, but its use has not been rigorously studied. Present evidence indicates an increased incidence of infection following steroid usage. The use of inhaled nitric oxide is still experimental.

5. **Treatment of underlying causes and other supportive measures** eg. nutrition, physiotherapy, antibiotics, etc.

PULMONARY EMBOLISM & DEEP VEIN THROMBOSIS

A. Aetiology

1. Majority of Pulmonary emboli arise from DVT in the iliofemoral system, others arise in the pelvic venous plexus as postsurgical or gynaecological complications.
2. Predisposing factors:
   - **a. General factors:**
   - Age >40.
   - Obesity.
   - Varicose veins.
   - Previous DVT.
   - OCP, pregnancy, puerperium.
   - Dehydration.
   - Immobility.
   - Surgery esp if > 30 min , abdominal or pelvic, orthopaedic to lower limb.
   - **b. Medical conditions:**
   - MI or heart failure.
   - Inflammatory bowel disease.
   - Malignancy.
   - Nephrotic syndrome.
   - Behcet's syndrome.
   - Homocystinuria.
   - **c. Haematological disorders:**
   - PRV.
   - Essential thrombocythaemia.
   - Myelofibrosis.
   - Paroxysmal nocturnal haemoglobinuria.
   - **d. Deficiency of anticoagulants:**
   - Antithrombin III.
   - Protein C or S.
   - Factor V Leiden mutation.
   - **e. Antiphospholipid syndrome.**

B. Clinical Features

1. Pulmonary embolism:

a. Symptoms:

- Dyspnoea of sudden onset, chest pain of substernal or pleuritic type, cough or haemoptysis, and apprehension (Pleuritic chest pain and haemoptysis suggest pulmonary infarction). Massive PE may present as cardiac arrest.

b. Signs - usually non-specific:

- Tachypnoea with shallow breaths, cyanosis, pleural rub, tachycardia, splitting of 2nd heart sound, right ventricular heave, S3, S4, high JVP, prominent 'a' waves, hypotension and shock in massive embolization.
- Clinical evidence of DVT present in 30% of patients with PE.

2. Deep vein thrombosis:

a. Symptoms:

- Most patients are asymptomatic or with minor leg discomfort or swelling only.

b. Signs:

- Signs include erythema & swelling of the leg, dilated superficial veins and calf discomfort on dorsiflexion of foot (Homan's sign).

C. Investigations

1. Diagnosis of DVT:

- In most instances, the diagnosis is based on good clinical history and classical signs.
- ***Doppler Ultrasonography-*** detects flow changes in veins, but is notoriously unreliable in detecting iliac vein and calf vein thrombi in asymptomatic patients. A negative test does not exclude a DVT.
- ***Contrast Venography***-most accurate diagnostic technique.
- ***Impedance Plethysmography-*** a non invasive technique sensitive for proximal, but not distal DVT.
- ***MRI.***

2. Diagnosis of pulmonary embolism:

- ***ECG*** - S wave in lead I, large Q wave in lead III, inverted T wave in lead III (SIQIIITIII) are not frequently seen. Other changes include non-specific ST depression and T wave inversion in anterior leads. P pulmonale, RBBB, and atrial arrhythmias may be seen. Most of these are ECG changes indicating right ventricular strain.
- ***CXR*** - Frequently normal. Focal pulmonary oligaemia (Westermark sign), localized infiltrates, Hampton's hump (a homogeneous wedge-shaped density based on pleura and pointing toward the hilum) consolidation, raised diaphragms, pleural effusion may be seen.
- ***ABG*** - Hypoxaemia, and hypocarbia due to tachypnoea.
- ***Echocardiography*** - May show dilated RV and hypokinesia. TR and PR may be seen. Rarely thrombus in the pulmonary artery may be visible.
- ***Ventilation/Perfusion Lung Scans*** - Should be performed in all clinically stable patients with suspected pulmonary emboli. It may shows ventilation -perfusion mismatch.
- ***Pulmonary Angiography***- should be performed whenever clinical data and noninvasive tests are equivocal or contradictory.
- ***CT scan (spiral)*** - May demonstrate thrombus within the proximal pulmonary arteries and may be a useful alternative in patients who are too unstable for pulmonary angiography.

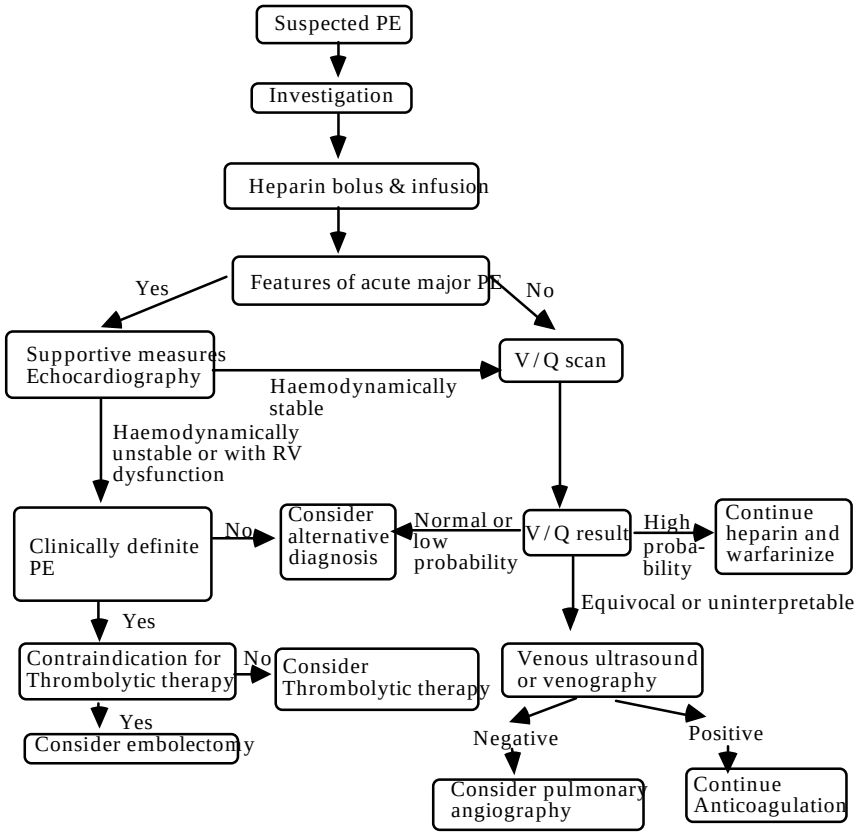
 # Locally, many of the tests mentioned above are not available and the diagnosis of PE is often made clinically together with some supportive lab tests available.

3. Investigations for an underlying cause, when appropriate:

- ***Coagulation screen.***
- ***Protein C, S, antithrombin III levels, lupus anticoagulant, false positive VDRL, anticardiolipin antibody, Ham 's test*** etc.
- ***Screen for malignancy*** - CXR, LFT, PSA, CEA etc.

D. Management of Pulmonary Embolism

Investigation and management of suspected pulmonary embolism



1. General measures:

- Bed rest with elevation of foot.
- Oxygen.
- Fluid infusion and inotropic agents for hypotension.

2. Definitive therapy for PE.

a. Anticoagulation:

- ***Heparin*** therapy should be started when the diagnosis of pulmonary emboli is suspected rather than delaying therapy until the diagnosis is certain.
- IV heparin should be given for the first 7-10 days. Oral warfarin should be initiated at the same time with an overlap of 3-7 days before heparin is discontinued. A standard beginning regimen consists of IV heparin 5000 U heparin bolus followed by 1000 U/hr. However, heparin delivered on a per weight basis could result in a shorter time to full anticoagulation, hence decreases the risk of recurrence. For heparin on a per weight basis, a bolus of heparin at a dose of 80u/kg can be given followed by an infusion of 18unit/kg/hour titrated individually to an aPTT of 1.5-2.5 times normal.

The first aPTT is obtained 4-6 hours after the start of treatment and then every 6 hours until the target range is reached.

- The starting dose of warfarin is 10mg/d, with subsequent doses adjusted based on the INR (refer to section on anticoagulation).
- ***Oral warfarin*** therapy should be continued for 3-6 months for PE, and indefinitely if 2 or more episodes of PE has occured. If unresolvable risk factors are present eg cancer, ATIII deficiency, protein C & S deficiency, antiphospholipid antibodies, warfarin should be continued for life.
- ***Low-molecular weight heparins (LMWHs)*** may provide effective alternative treatment for PE and is as effective and safe as traditional IV heparin. Dosage is as in treatment of DVT.

b. ***Systemic thrombolytic therapy*** with streptokinase, urokinase or tissue plasminogen activator hastens the resolution of thrombi.

- May be indicated in patients with massive embolism and persistent systemic hypotension despite appropriate supportive measures. In extreme circumstances, when there is a high suspicion of PE in a critically ill patient, thrombolysis may be given empirically.
- ***Streptokinase*** can be given as IV infusion 250,000-500,000U over 30 min, followed by streptokinase infusion 100,000U IV hourly for 24 hrs. Concomitant heparin therapy is not recommended and if started previously, the heparin should be stopped and resumed after thrombolytic administration without a bolus.
- ***rtPA*** can be given at a dose of 100mg infused over 2 hours.
- No tests of coagulation are needed during infusion of any of the thrombolytic agents.

c. ***Inferior vena cava (IVC) filter:***

- May be considered in ***(i) Recurrent PE despite adequate anticoagulation (ii) Inability to tolerate anticoagulation (iii) Immediately following pulmonary embolectomy.***

d. ***Pulmonary embolectomy:***

- May be considered only in rare patient with angiographically proven PE ***(i) who remains in shock despite thrombolytic therapy and supportive care (ii) in whom thrombolytic therapy would be appropriate but is contraindicated.***

3. Management of shock or cardiac arrest due to pulmonary embolus:

- The most logical approach for patients in cardiopulmonary shock or arrest, assuming that thrombosis has been documented either in the lungs by angiography/perfusion scan or in the lower extremities by venography or noninvasive studies, is to start thrombolytic therapy as soon as possible and to provide appropriate circulatory support with fluids and pressors.
- If available, cardiopulmonary bypass and embolectomy should also be considered.

E. Management of Deep Vein Thrombosis

1. **Bed rest** with elevation of the leg for 24-48 hours.

2. **Analgesia** with an NSAID if needed.

3. **Anticoagulation:**

- Heparinized patient as in pulmonary embolism.
- In DVT ***heparin therapy*** can be started when clinical suspicion of DVT is high and this may be discontinued if subsequent investigations are negative.
- ***Warfarin*** should be started during heparin therapy as in pulmonary embolism and overlap for 3-7 days. Keep INR between 2.0-3.0. Heparin can then be stopped provided INR is >2.
- Warfarin is usually given for 3 months after a first DVT (INR 2.0-3.0), and 1 year for those with history of previous DVT. Indefinite treatment may be indicated after recurrent (>2 episodes) thromboembolism (INR 3.0-4.5). If unresolvable risk factors are present eg cancer, ATIII deficiency, protein C & S deficiency, antiphospholipid antibodies, warfarin should be continued for life.
- The use of SC heparin in treatment of DVT is as safe as continuous heparin. SC heparin can be given 15000U 12hrly and aPTT taken 6 hrs after SC injection should be kept at 1.5-2.5 times the control level.
- ***Low-molecular weight heparins (LMWHs)*** produce predictable response when given in fixed doses based on patients' body weight. Labarotory monitoring is not necessary. They are more effective than adjusted-dose unfractionated heparin. LMWHs are gradually replacing heparin in the initial treatment of DVT.
- ***Nadroparin Ca*** can be given at a dose of 0.1ml/10 kg (0.1ml = 2,500 AXa Units) body wt SC bd (min 0.5ml for those with BW <50kg, max 1ml for those with BW >90kg) given SC in the abdominal wall for 10 days. Warfarin should be instituted as in unfractionated heparin.
- ***Enoxaparin Na*** can be given at a dose of 1mg/kg SC twice daily.

4. **Thrombolytic therapy:**

- May be indicated in patients with extensive, large-vein DVT (eg. iliofemoral). Dose as in PE.

5 Inferior vena cava (IVC) filter:
- May be considered in the present of large, free-floating thrombus in the ileo-femoral veins.

6. Look for the cause of the DVT.

PNEUMOTHORAX

A. Causes

a. Traumatic:
- Penetrating chest wounds.
- Iatrogenic (chest aspiration, intercostal nerve block, subclavian cannulation, transbronchial biopsy, needle aspiration lung biopsy, positive pressure ventilation).
- Chest compression injury (including external cardiac massage).

b. Spontaneous:
1. Primary (most common causes).
2. Secondary:
- COPD.
- Asthma.
- Congenital cysts and bullae.
- Pleural malignancy.
- Rheumatoid lung disease.
- Bacterial pneumonia.
- Tuberculosis.
- Whooping cough.
- Cystic fibrosis.
- Histiocytosis X.
- Tuberous sclerosis.
- Marfan's syndrome.
- Sarcoidosis.
- Oesophageal rupture.
- Pneumocystis carinii pneumonia.

B. Clinical Features

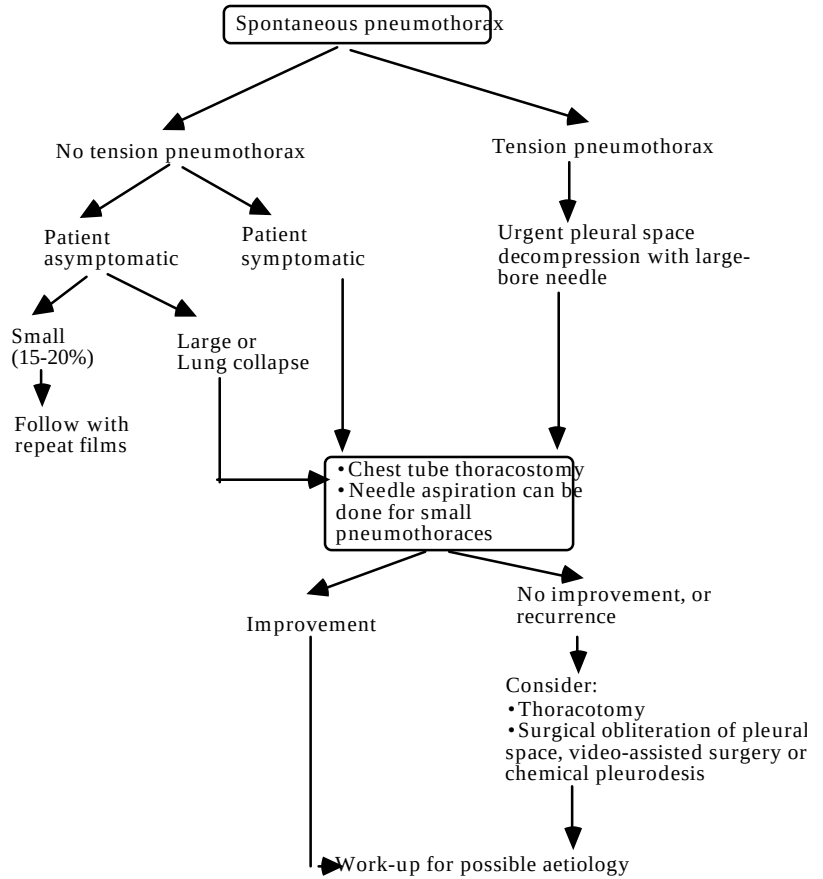
- Most commonly chest pain on the side of the pneumothorax and dyspnoea. Chest pain is sharp and pleuritic.
- Dypnoea, tachycardia and tachypnoea in large pneumothorax.
- Physical examination shows decreased breath sounds and hyper-resonance of the affected side. Other findings may include subcutaneous emphysema of the neck and chest wall.
- In tension pneumothorax - tracheal deviation, cyanosis and jugular veneous distension.

C. Diagnosis

- In the stable patient a CXR confirms the diagnosis. The expiratory chest film is most sensitive.
- If tension pneumothorax is suspected, immediate treatment with needle thoracostomy is indicated before any diagnostic studies.

D. Management

1. Algorithm for treatment of spontaneous pneumothorax:



2. Tension pneumothorax:

- If tension pneumothorax is present, insert the largest cannula to hand into the ***second intercostal space in the midclavicular line*** on the side with absent or reduced breath sounds; if air rushes out, leave the cannula in place until a chest drain is inserted.
- Insert an ***intercostal drain*** immediately.

3. Small asymptomatic or mildly symptomatic pneumothoraces (<15-20%) can be treated with cough suppression and analgesics.

- These patients may be followed as outpatients with frequent chest films (repeat CXR 1-2 days later), although some centres admit these patients for observation.
- The patient can resume normal activity but avoid strenous exercise.
- Air will be reabsorbed at a rate of 1.25% of the total radiographic volume of the hemithorax per day.

4. Symptomatic patients or asymptomatic patients with large pneumothoraces:

- ***Needle aspiration*** of pneumothoraces speeds the removal of pleural air in symptomatic patients or asymptomatic with large pneumothoraces without evidence of continued air leaks.
- Simple aspiration entails placement of a small catheter (often an IV catheter) between the fourth and fifth intercostal space over the superior rib margin in the mid axillary line after appropriate sterile preparation and anaesthesia. A three-way stopcock and a large syringe are used to aspirate intrathoracic air with full lung expansion heralded by the inability to aspirate further air or by sudden cough. The catheter is then removed.
- Alternatively, chest tube thoracostomy can be done.

5. Significantly symptomatic patients with large pneumothoraces:

- ***Admit and treat with chest tube thoracostomy*** patients who have significant symptoms and large pneumothoraces.
- ***A small-bore catheter*** (up to 18F) can be safely used as the initial therapy in all patients with an ***spontaneous pneumothoraces,*** provided the patient is not at significant risk for a large air leak (receiving mechanical ventilation or likely to be given mechanical ventilation) or catheter occlusion (presence of pleural effusion).
- ***A larger-bore tubes***, ≥22F should be used in a patient at risk for ***mechanical ventilation or with accompanying pleural fluid.***
- For thoracotomy, the best approach is usually the ***third or fourth space in the midaxillary line.*** This is less alarming for the patient and there is less muscle to be crossed than with the second space in the midclavicular line.
- Place chest tubes under water seal drainage.
- ***Apply suction*** (start with 5kPa & titrate as tolerated) in patients with ***active air leaks and/or significant lung collapse***, and administer nasal oxygen to enhance the resorption of pleural air.
- Pulmonary oedema is a rare complication of re-expanded lung, occuring primarily in lungs collapsed for more than 3 days.

6. Continued air leaks:

- Place additional chest tubes or/and continuous suction in patients with continued air leaks.
- Consider thoracotomy in patients in whom this treatment fails after 7-10 days.

7. Recurrent spontaneous pneumothoraces:

- Consider patients with recurrent spontaneous pneumothoraces (2 or 3 recurrences) for chemical pleurodesis (using tetracycline, bleomycin or talc), video-assisted thoracoscopy or surgical obliteration of the pleural space.

8. Removal of chest tube:

- The chest tube can be left in place for 24 h after the air leak subsides and the lung reexpands. Then the tube may be clamped for an additional 24 h and removed if recurrence does not occur.

- However, clamping times as short as 4 h have been used with success.

9. **Surgical intervention** should be considered if:
- The lung fails to reexpand on chest tube drainage.
- There is history of two or more previous pneumothoraces on the same side as the current episode.
- Any occurrence of bilateral pneumothorax.

10. For all patients with a first episode of pneumothorax, there should be a diagnostic investigation into the **aetiology.**

3. NEPHROLOGY

_ ACUTE RENAL FAILURE

A. Causes

a. Prerenal causes:

i) Volume depletion:

- Blood loss or fluid loss (N.B. Beware "non visible" third space loss as occurs in septic shock).

ii) Reduced cardiac output:

- Cardiac failure, cardiac tamponade, etc.

iii) Vascular obstruction:

- Bilateral renal artery occlusion eg. thrombosis, dissecting aneurysm.

b. Intrarenal causes:

i) Glomerulonephritis.

ii) Vasculitis:

- eg. SLE.

iii) Vasocontrictive diseases:

- eg. Malignant hypertension.
- Haemolytic-uraemic syndrome.

iv) Acute interstitial nephritis:

- Drug related.
- Systemic infections eg. leptospirosis.

v) Intratubular obstruction:

- eg. uric acids, oxalates crystals.

vi) Acute tubular necrosis (ATN):

- Nephrotoxins:
  Drugs: Amphotericin B, aminoglycosides, radiocontrast, etc.
  Poisons: Ethylene glycol, methanol, heavy metals.
  Ischaemia: Any cause of hypotension.

c. Postrenal causes:

i) Surgical obstruction at pelvic, ureteric or bladder neck.

B. Investigations in acute renal failure

_ ***Tests are done to :***

a. confirm the the functional diagnosis of acute renal failure

b. define immediate life threatening or potentially life threatening events

c. delineate the possible aetiologic basis and

d. monitor the progress of the functional derangements, with treatment.

a. Functional diagnosis:

- Full blood count and film.
- Blood urea, creatinine.
- Urinalysis and urine output determination.

b. Defining life threatening events:

- Chest X ray for pulmonary oedema.
- Serum electrolytes and ECG for dangerous hyperkalaemia.
- Blood gas for life threatening acidosis.

c. Delineate the possible aetiology:

- Ultrasound for renal sizes, hydronephrosis, stones, etc.
- Collagen screen eg. ANF, LE cells to exclude SLE.

- Urinary oxalate crystals for ethylene glycol poisoning.
- Occasionally renal biopsy to exclude rapidly progressive glomerulonephritis.

d. Monitor progress of disease:

- Repeat urea, serum potassium, arterial blood gases, CXR, ECG, etc.

Urinary Profiles in Pre-renal and intrinsic renal failure

Index	*Prerenal*	*Intrinsic renal*
• Sediment	Normal	Tubular cells, cell cast, granular casts
• Specific gravity	High 1.020	Fixed at 1.010-1.012
• Sodium	Low < 20mmol/l	High > 40mmol/l
• Fractional excretion of sodium	< 1%	> 1%
• U:P urea ratio	> 20	< 10
• U:P creatinine ratio	> 40	< 20
• U:P osmolality ratio	> 1.2	< 1.2
• Osmolality > 500		< 400

C. Management of acute renal failure

I. Strategy

1. ***Identify the functional derangement.*** This requires a high index of suspicion. (N.B. Beware of non-oliguric acute renal failure)
2. ***Define and neutralise immediate life threatening or potentially life threatening events*** eg. Pulmonary oedema, hyperkalaemia, severe acidosis
3. ***Delineate the cause***. Remember to exclude a surgical obstruction
4. ***Plan long term management*** such as preventing future identical insults, etc

II. Conservative medical management

1. Fluid management:

- One of the hallmarks of acute renal failure is a marked reduction in urine production (<400 mls/24 hours). However, non-oliguric renal failure can also occur.
- In established renal failure, the strategy is fluid restriction. However, in the pre-renal phase, fluid replacement and correction of intravascular volume contraction is important.
- ***Accurate clinical judgement of intravascular volume*** is required. Assessment of intravascular volume can be achieved by:

i. Estimating from history the quantum of loss.
ii. Determining loss in body weight.
iii. Assessing clinically the percentage of dehydration eg. skin tugor, etc.
iv. Measuring the pulse volume and blood pressure.
v. Putting in a central line to measure central venous pressure (CVP).

- Hypovolaemia should be corrected . Any hypotension must be quickly corrected with fluid challenge, or if there is no volume deficit, the use of an appropriate inotrope is advocated.
- ***Patient with volume deficit:***

I. IN HYPOTENSIVE PATIENTS:

- ***Fluid challenge*** with 250 ml of normal saline over 15 mins may be given. If CVP measurement does not increase by 2 cm repeat fluid challenge (up to 500-1000ml of NS may be required). Stop if CVP measurement increase to satisfactory level ie 5-10cm H2O *(NB:-Patient in severe shock may have an initial high CVP due to central venous spasm).*
- If a good blood pressure is obtained, and good urine flow is established (>40 mls/hour), continue with a slower fluid replacement regimen.
- If volume is restored, and blood pressure is still low, use an appropriate inotrope (eg dopamine titrated to less than 10 mcg/kg/min).
- If volume is restored, with good blood pressure, but urine outflow is poor (less than 40 mls/hour), start IV frusemide as described below.
- IV frusemide can be given either by slow bolus of 40-120mg repeated as necessary or infusion (dilute in NS) at a rate of 10-60mg/hr with maximal daily dose of 2g. Large doses of IV frusemide for prolonged period may cause hearing loss.
- If volume is restored, with good blood pressure, and the use of both frusemide and inotrope do not induce adequate urine output, restrict fluid to 500 mls/24 hours plus measured losses. Avoid potassium and food rich in potassium. Keep a strict intake and output chart.

II. IN NORMOTENSIVE PATIENTS:

- Fluid challenge should also be given to correct fluid deficit. If good urine flow is established (>40ml/hr), continue with slower fluid replacement regimen. If volume is restored but urine outflow is poor (<40ml/hr), start IV frusemide as described above.

- ***Patient without volume deficit:***
  Start IV frusemide and if necessary with an inotrope as above. If urine flow cannot be induced, restrict fluid.

2. Dietary modification:

- ***Protein*** - 0.5gm/kg/day (normal to high protein intake if dialysis is in place).
- ***NaCl*** - 2-4g/day.

- ***Calaric intake*** - 35-50 kcal / kg / day.
- ***Potassium*** - 40mmol / day (if dialysed).
  N.B. Nutrition is a vital area of management and should be given a high priority.

3. Blood pressure:
- ***Hypotension*** should be corrected with volume expansion or vasopressors, depending on the patient's intravascular volume status.
- ***Hypertension*** should be treated appropriately, with the blood pressure controlled at a rate depending on the clinical situations.

4. Hyperkalaemia should be treated promptly (see section on hyperkalaemia). Successful diuresis or dialysis are the only definite methods of removing potassium from the body; all other methods shift potassium between body fluid compartments.

5. Metabolic Acidosis:
- ***Metabolic acidosis*** of pH <7.2 or with HCO3 <10mmol / l should be treated with NaHCO3. A rough estimation of the amount required can be calculated from the following formula:

  0.5 X Body weight (kg) X Base deficit

  # 1ml of 8.4% NaHCO3 provides 1 mmol/l of NaHCO3.
  # Base deficit = 24 - Actual HCO3.
- In practice the treatment is usually 'titrated' slowly by infusing bicarbonate (eg. 1ml of 8.4% NaHCO3 per kg BW over 30 min) and regularly checking the plasma pH & HCO3. It is safer to under correct the deficit.

6. Drug dosages:
- Dosages of agents excreted by kidney must be adjusted for the level of renal function. Refer to drug information documents for accurate dosing.

7. Infection:
- Appropriate antibiotics should be given. Irrespective of the degree of renal impairment or the route of drug metabolism, a "loading" dose is mandatory, followed by appropriate adjustment in dosage / frequency of dosing, to maintain a therapeutically efficacious and safe level.

8. Gastrointestinal haemorrhage should be treated appropriately. Prophylaxis with H2 antagonist or similar drugs may be given.

9. Anaemia: Packed cells are transfused when anaemia is symptomatic. Aim for slow correction to a "functionally accepted level" rather than a normal level.

10. Hyperalimentation:

- In hypercatabolic patient, hyperalimentation should be started when the patient is more stable.
- If instituted in oliguric patients, it will necessitate more frequent dialysis or some of the continuous dialysis hemofiltration methods.
- The best and safest feeding route is oral; tubes placed in the intestinal tract are less desirable; IV feeding is the most dangerous.

11. Other measures:

- Abdominal ultrasound should be done to measure renal size and exclude obstructive uropathy.
- A renal biopsy may be indicated to establish a treatable renal cause, if pre- and post-renal causes and abdominal infection have been excluded.

III. Dialysis

- Dialysis is best started early (eg when BU is around 35 mmol/l and creatinine around 600 umol/l).
- Dialysis is most often prescribed every other day or as frequently as necessary.
- In severely catabolic patients (crush injury, burns), daily dialysis (usually haemodialysis) may be required.
- It is generally accepted that in patient with ARF, dialysis therapy should be used as often as necessary to maintain BU of <30mmol/l.

1. Indications for initiating dialysis are:

- BU >35mmol/l.
- Severe hyperkalaemia (>6.5mmol/l).
- Severe metabolic acidosis (pH <7.2).
- Volume overload +/- pulmonary oedema not responsive to diuretics.
- The development of uraemic symptoms eg. CNS (asterixis, neuromuscular irritability, somnolence, coma, seizures), GI (nausea and vomiting, haemorrhage) symptoms.
- Oliguria (urinary output <5ml/kg per day) or anuria (no urinary output for 12 hr).

N.B. Do not wait for the "critical number" to appear before initiating dialysis if the renal function is deemed to deteriorate. Early dialysis results in lessmorbidity and mortality.

2. Type of dialysis:

- The type of dialysis therapy for a particular patient - haemodialysis vs peritoneal dialysis - depends on the clinical situation.
- Patients with severe tissue breakdown (eg. rhabdomyolysis, trauma, burns, sepsis, postoperative) have enhanced urea production and usually require haemodialysis.
- In other types of ARF in which the catabolic component is less prominent, peritoneal dialysis may be adequate.

IV. Treatment of specific conditions

1. Acute intersititial nephritis.

- The suspected causative agent(s) should be stopped.
- When renal impairment is minor, recovery is the rule, and dialysis is usually not indicated.
- In more severe cases, high dose, short term prednisolone therapy (60mg/day for 1-2 weeks) may speed recovery of renal function.
- Renal function replacement therapy may occassionally be necessary

2. Primary renal disease, systemic diseases and vascular diseases.

Disease	Therapy
Acute poststreptococcal glomerulonephritis	No specific therapy unless very severe. Penicillin therapy indicated for 10 days
Goodpasture's syndrome/anti GBM GN	Plasmapheresis + Pulse IV methylprednisolone 1g daily for 3 days followed by prednisolone 1g/kg/day and cyclophosphamide 2 mg/kg/day
Pauci-immune rapidly progressive GN (ANCA associated microvasculitis)	IV pulse methylprednisolone followed by oral prednisolone 1 mg/kg/day and cyclophosphamide 2 mg/kg/day
SLE	Prednisolone 1-2mg/kg/day with or without initial IV methylprednisolone 1g od for 3 days +/- cyclophosphamide 2 mg/kg/day or azathioprine 2-3mg/kg/day
Subacute bacterial endocarditis	Antibiotics (note use of possible nephrotoxic antibiotics)
Henoch-schonlein purpura	No specific therapy
Malignant hypertension	Antihypertensives. Control blood pressure to a safe but NOT normal level within a twenty four hour period. Dialysis, if required

D. Footnotes

1. D Cockcroft formula:

Creatinine clearance (ml/min)

$$= \frac{(140\text{-age in years}) \times (\text{wt in kg}) *}{72 \times \text{serum creatinine in mg/dl}}$$

* For women multiply by 0.85

2. **Fractional excretion of sodium (FENa)** is the per cent of the filtered sodium which is eventually excreted.

$$FENa\ (\%) = \frac{\text{Urine Na}}{\text{Plasma Na}} \times \frac{\text{Plasma creatinine}}{\text{Urine creatinine}} \times 100$$

In normal subject FENa is <1%.

_ PERITONEAL DIALYSIS

- ***Peritoneal dialysis*** is approximately one-eighth as efficient as haemodialysis in altering blood solute composition and about one-fourth as efficient in terms of fluid removal. However, measured over a longer period, the efficacy of haemodialysis in effecting changes in solute and fluid status is not markedly different from that of peritoneal dialysis.

A Indications

a) Acute Renal Failure.
b) Removal of toxic substance/poison, predominantly excreted via the kidneys
c) Fluid overload eg. in CCF if use of diurectics produce unsatisfactory results because of underlying renal impairment.

B. Contraindications

a) Absolute: Ileus , presence of obvious intra-abdominal adhesions.
b) Relative: Recent "dirty" abdominal surgery, presence of an intraabdominal vascular graft.

C. Peritoneal Dialysis Catheter Insertion

1. **Consent** must be obtained and peritoneal dialysate and tubing ready prior to insertion of peritoneal catheter. Choose appropriate gauge.

2 **Position of patient:**
- Supine with empty bladder unless very orthopnoeic.

3. Technique:

a) ***Shave, prep and drape***.
b) ***Infiltrate Local Anaesthetic.***
- Infiltrate 2 inches below umbilicus in midline from skin to peritoneum (Whole length of a 21 G needle).
- Alternative sites to avoid abdominal scar: supra umbilical, midline or right/left lower quadrant lateral to rectus sheath on a line joining the umbilicus to the anterior superior iliac spine.

c) Make ***incision*** with blade (Bard-Parker 10) - about 5 mm wide and through the whole skin thickness.
d) ***Position PD catheter*** with stylette in incision. Keep catheter in midline, perpendicular to abdominal wall.
e) Ensure that ***stylette*** protrude 1/8 inches from tip of catheter.
f) Instruct ***patient to lift head*** to tense abdominal wall (If necessary, staff to raise patient's shoulders).
g) ***Insert PD catheter*** into peritoneal cavity. Use both hands, one to provide force and the other to prevent excessive penetration. (In some patients, A14G cannula is inserted through the anaesthetized area into the peritoneal cavity and 1-2 litres of dialysate rapidly infused through this to distend the abdominal cavity so that its contents will float out of the way when the PD catheter is inserted The cannula is then removed and a small incision is made at the puncture site which should be large enough to just admit the PD catheter).
h) Upon ***entering the peritoneal cavity*** (a "give" is felt), withdraw stylette slightly so that its tip is flushed with the end of the catheter. Redirect catheter towards right or left iliac fossa .Gently advance catheter until a resistance is met. Withdraw the catheter about half to one inch. Remove stylette. A free flow back of peritoneal fluid into the catheter, and a unimpeded "swing" with respiration indicate the catheter is intraperitoneally placed.
j) ***Trim catheter*** to allow only 2 inches to protrude from abdominal cavity.
k) ***Fix catheter position***
- Slide fixation clamp (correct side up) to abdominal wall - secure with skin suture.

l) ***Apply dressing:*** sterile gauze dressing around catheter and then apply elastoplast to cover dressing.
m) Secure dialysis tubing and ***begin dialysis.***

D Peritoneal Dialysis Regime

1. Use either ***0.5 litre*** (smaller patients, patients with pulmonary disease, patients with hernia) or ***1 litre*** (average-sized adult) ***isotonic (1.5%)*** or ***hypertonic (4.24%)*** solution per cycle per hour.

- The greater the volume used, the higher will be the clearance and the ultrafiltration rate.
- 1.5% Dextrose is used as a 'standard' prescription. This amount of dextrose will exert an osmotic force sufficient to result in the removal of 50-150ml fluid / hour when using a 1-liter exchange and a 60-minute cycle time ie 1200-3600 ml / day.
- Higher concentrations of dextrose is used when a higher rate of fluid removal is required eg. alternating 4.25% dextrose with 1.5% dextrose.
- When very rapid fluid removal is required eg. in pulmonary oedema. 2-3 in-out (zero dwell time) 1-litre exchanges of 4.25% can be used. Each exchange will remove approximately 300 ml of fluid, so that almost 1000ml can be removed over 1 hour period.

2. In the ***first 3 cycles,*** PD fluid is to be infused in and allowed to run out fast without any indwelling time. A quick inflow and outflow indicate good patency and good intraperitoneal catheter placement.

3. Following this dialysis is commenced with each cylce over an hour:
- ***10 minutes*** for infusing in ***(inflow time)***, ***20 minutes*** for the fluid to stay inside the peritoneum ***(dwell time)***, and ***30 minutes*** for infusing out ***(outflow time).***
- ***Shorter dwell period*** for high-efficiency dialysis can be used for the short term in patients who are ***extremely hypercatabolic, when rapid fluid removal is required and for patients with peritonitis or damaged peritoneal membrane*** eg. Inflow 10 mins, Outflow 10 mins, and Dwell 10 mins.

4. 500 units heparin / litre dialysate is to be added for the first 4 cycles and into every 4th cycle. If the returning dialysate is blood stained or cloudy because of fibrin, hourly heparin is indicated.

5. Appropriate measures need to be taken if:
   a) The fluid infused out is heavily blood stained.
   b) The fluid infused out is turbid.
   c) The fluid infused out is less than 500 mls.

6. In most cases the dialysis should be continued for ***48-72 cycles.***

7. Routinely, the 1st, 20th and 40th cycle of peritoneal dialysate infused out, and, at termination of dialysis, the catheter tip, should be sent for culture.

8. The ***BUSE*** should be checked at least twice a day.

9. If the ***serum potassium*** is less than 4 mmol / L, 0.3 g of potassium chloride is to be added to each litre of dialysate fluid.

E Other aspects of Nursing Care.

1. 2-4 hourly vital signs i.e. Blood Pressure, pulse, respiratory rate and temperature. Observe for any discomfort and pain (More frequent if active bleeding suspected).
2. Check for any leakage from the peritoneal catheter site.
3. Check for good constant inflow and outflow.
4. Record the inflow and outflow of every cycle on a chart on a cumulative basis. Note the nature and colour of the fluid infused out. Monitor also the total fluid exchange, urine output, intake, etc
5. The peritoneal catheter site should be redressed aseptically daily or when soaked. Look for signs of infection and tenderness.
6. Inform the doctor immediately if there are any abnormalities.

F Troubleshooting for problems with acute peritoneal dialysis

Problem	Probable cause	Action plan
Exit site leak	1 Long skin incision	1 Tighten pursestring
Poor inflow or outflow	1 Catheter problem	1 Exclude kinking of catheter or lines Alter position of patient eg lie on one side Treat constipation Reposition catheter tip
	2 Clot in catheter	2 Flush and add heparin to dialysate
	3 Omental wrapping	3 Flush and reposition. Replace catheter if necessary.
Pelvic pain	1 Pressure from catheter tip	1 Treat constipation 2 Replace catheter
Abdominal pain	1 Stretching of peritoneum	1 Exclude peritonitis 2 Dialysed on a smaller volume
Faeculent effluent	1 Viscus perforated by catheter	1 Off PD. Rest abdomen for _ 2 wks before resuming PD. Start systemic antibiotics. Laparotomy if fails to resolve. Alternate dialysis procedure might be indicated.
Bloody effluent	1 Blood vessels damaged by catheter	1 Tighten pursestring. Consider cryoprecipitate / FFP or DDAVP. Continue rapid cycle with heparin till clear. Off PD if fails to resolve and consider laparotomy.
Unilateral pleural effusion	1 Pleuro-peritoneal fistula	1 Confirm diagnosis (high sugar content of pleural aspirate) and switch to haemodialysis.
Poor metabolic control	1 Hypercata-bolism	1 Switch to haemodialysis treatment
Hyperglycaemia in diabetic patients	1 High dextrose solution	1 Add regular insulin to dialysate • 4-5 units in each liter of 1.5% Dextrose • 7-10 units in each liter of 4.25% Dextrose to keep blood sugar below 12 mmol / litre *or* 2 Subcutaneous insulin

Peritonitis	1 Bacterial infection 2 Rarely fungal, viral or chemical	1 Send the first cloudy dialysate sample for Gram stain, culture and cell count (with EDTA bottle)* 2 Lavage peritoneum with rapid exchanges with heparin added to dialysate for 4 bags 3 Resume hourly exchanges & add intraperitoneal antibiotics every cycle # • Gentamicin[1] 8mg/l + cloxacillin [2]100mg/l 4 Heparin 500u/l every cycle till effluent clear 5 May need to change antibiotics according to C & S 6 Off PD & change to HD if peritonitis persisted or worsened with continue PD. 7 Change to systemic antibiotics for at least 1 wk after stopping PD. * The percentage of neutrophils does not normally exceed 15% of non erythrocyte cell count. A neutrophil % of >50% strongly suggests peritonitis. # In patients who appear very ill, administer a dose of IV loading antibiotics prior to IP antibiotics. **1** ***Alternative antibiotic:*** Amikacin 6-8mg/l **2** ***Alternative antibiotics:*** Cefoperazone 250mg/l Ceftazidime 125mg/l Cefuroxime 250mg/l Cefotaxime 250mg/l Vancomycin 25mg/l

3.12

Nephrology

4. GASTROENTEROLOGY AND HEPATOLOGY

_ HEPATIC ENCEPHALOPATHY

- The syndrome of altered consciousness and neuropsychiatric disturbances seen in patients with severe liver failure.
- It may be acute, as in acute / fulminant liver failure, or chronic and recurrent, as in liver cirrhosis; cerebral oedema is more important in the encephalopathy of acute / fulminant liver failure, while portosystemic shunting and hepatocellular dysfunction are implicated in the portosystemic encephalopathy of cirrhosis.
- It is critical to distinguish portosystemic encephalopathy (PSE) from acute / fulminant liver failure since there are a number of effective therapeutic interventions in the treatment of PSE, whereas the management goal in fulminant liver failure is to support the patient until hepatic regeneration occurs or transplantion is performed.

A. Factors in hepatic encephalopathy

Type of encephalopathy	Aetiological factor
Acute liver failure	Drug reaction and overdose eg. para-cetamol, halothane, antituberculous drugs Viral hepatitis Pregnancy Sepsis Alcoholic hepatitis Reye`s syndrome
Portal-systemic encephalopathy	Diuresis, dehydration, paracentesis, surgery, haemorrhage, sedatives, infection, hypokalaemia, high-protein diet, constipation

B. Symptoms and Signs

1 Acute fulminant liver failure:

- The diagnosis of acute fulminant liver failure depends on the recognition of hepatic encephalopathy within 8 weeks after the onset of an acute liver illness and in the absence of any feature of chronic liver disease.
- ***Features:*** Malaise, nausea, vomiting, fever, headache, abdominal pain, jaundice, fetor hepaticus, changes in personality eg. antisocial behaviour and character disturbance, delirium, fits, clouding of consciousness, asterixis, increased muscle tone and brisk reflexes.

- Later, decerebrate spasticity, dysconjugate eye movements, skew positions of the eyes, respiratory and circulatory failure with hypotension, cardiac arrhythmias and respiratory arrest.
- Ascites develops late and splenomegaly is unusual.

2. Portal systemic encephalopathy (PSE):

- In mild PSE, the symptoms and signs are so subtle as to be overlooked by patient and family members and consist of slight postprandial confusion or somnolence. Recognition of this condition requires careful observation and neuropsychological testing.

- ***Features*** are:
  - ***Disturbed consciousness*** - hypersomnia, reversal of normal sleep pattern, fixed stare, apathy, slowness and brevity of response, coma, and delirium.
  - ***Personality changes*** - childishness, irritability, and euphoria.
  - ***Intellectual deterioration*** – slight impairment of mental function to gross confusion, constructional apraxia, and astereognosis.
  - ***Speech*** – slow, slurred, monotonous speech, and dysphasia.
  - ***Others*** – jaundice, fetor hepaticus, asterixis, spider naevi, palmar erythema, clubbing, gynaecomastia, testicular atrophy, splenomegaly, bruises, hypertonia, muscle twitching, ankle clonus, extensor plantar in deep coma, hyperventilation, hyperthermia, grasping and sucking reflexes.
- The clinical course fluctuates and frequent observation is necessary.
- Diagnosis is clinical and routine liver biochemistry merely confirms the presence of the underlying liver disease.

West Haven criteria for grading of hepatic encephalopathy

Grade I	Confusion, altered mood and behaviour
Grade II	Drowsy, inappropriate behaviour
Grade III	Stuporose but obeys simple commands; slurred speech, marked confusion
Grade IV	Unarousable coma

C Investigations

1. ***In acute liver failure:*** Consider FBC, PT, BUSE, ABG, creatinine, liver function test, blood sugar, virology (HAV IgM, HBsAg, EBV, CMV, HSV), toxicology (eg. paracetamol level), autoantibodies (eg. ANA, SMA, AMA, LKM antibodies), septic workup, serum caeruloplasmin & urine copper if <50 years, ECG, chest X-ray, ultrasound abdomen, and CT Brain.

2. ***In chronic liver disease:*** FBC, PT, BUSE, ABG, creatinine, liver function test, blood sugar, ECG, CXR, CSF examination if suspected meningitis, electroencephalogram, CT brain & psychometric testing.

D Differential diagnosis

- Mainly for hepatic encephalopathy in chronic liver disease - this includes:
  Delirium tremens
  Wernicke`s encephalopathy
  Alcoholic intoxication
  Subdural haematoma
  Functional psychosis
  Metabolic encephalopathies - hypoglycaemia, ketoacidosis, uraemia, hyponatraemia, hypoxia / anoxia, hypercapnoea

E. Management

I. Acute liver failure

1. General measures:

- Accurate assessment of the aetiology and complications of fulminant liver failure is central to the general management of these patients.
- Prevention and early detection and treatment of the numerous complications is of paramount importance.
- These patients should be managed in an intensive care unit.
- A central venous line, an arterial line, an indwelling urinary catheter and a nasogastric tube should be inserted.
- Oxygen supplementation may be required; intubation and ventilation if grades III or IV encephalopathy.
- Hb, BUSE, creatinine, PT, blood sugar and ABG should be monitored regularly.
- The patient's vital signs and cardiac rhythm should be monitored closely.
- Avoidance of sedative drugs and narcotics. However, in patients with delirium or convulsions, IV diazepam may be used cautiously.
- Normovolaemia should be maintained. Fluid overload may precipitate or worsen cerebral oedema, and hypovolaemia may result in hypotension with disastrous effects on the liver, and other organs.
- Omeprazole 40mg od or Sucralfate 1g qid should be given to prevent stress ulcer.

2. Specific management:

- This includes early treatment of paracetamol overdose with N-acetylcysteine infusion (see section on paracetamol poisoning), mushroom poisoning with forced diuresis and activated charcoal, herpesvirus infection with acyclovir and acute hepatic vein occlusion with surgery or transjugular intrahepatic portosystemic shunt.
- Liver transplant improves survival of patients with acute liver failure to between 65% and 90% at 1 year.

- Medically, uncontrolled intracranial hypertension, severe sepsis and adult respiratory distress syndrome are considered contraindications.

3. Management of complications:

a. Cerebral complications:

- Both encephalopathy and cerebral oedema occur in patients with fulminant liver failure.
- Signs of increased intracranial pressure should be monitored (An extradural sensor is helpful if available).
- In advanced liver failure with increased ICP, provided renal function is adequate, treatment with mannitol (0.25-0.5 g/kg), repeated until a plasma osmolality of 320 mosm is reached, should be instituted.
- It is important to note that mannitol therapy will require haemofiltration or haemodialysis in the setting of renal failure, with the removal of 2 - 3 times the volume infused.
- Other measures include hyperventilation to keep PCO_2 25-30mmHg, thiopentone induced barbiturate coma and etc.

b. Cardiovascular system:

- Patients have an elevated cardiac output and a lowered systemic as well as pulmonary vascular resistance; this is similar to the pattern seen in patients with sepsis and burns which leads to systemic hypotension.
- Swan Ganz catheter as well as intraarterial line monitoring may be appropriate in severe cases; the PCWP should be maintained at 8-12 mmHg with colloid infusions.
- Hypotension may require treatment with vasoconstrictors, such as noradrenaline and dopamine.

c. Renal complications:

- Oliguric renal failure occurs in up to 50% of cases irrespective of aetiology and is associated with a worse prognosis.
- Management of renal dysfunction requires adequate volume replacement (balanced against the risk of aggravating cerebral oedema) and avoidance of nephrotoxic agents and arterial hypotension.
- Low dose dopamine (2 - 5 mcg/kg/min) is often used.
- Renal replacement therapy may still be indicated and the indications for haemofiltration are fairly standard: fluid overload, hyperkalaemia, acidosis, rising creatinine and following mannitol infusion if oliguric.
- Continuous haemofiltration is the preferred method of renal replacement as intermittent treatment is associated with an abrupt increase in ICP.

d. Respiratory complications:

- Most patients who develop grade III & IV encephalopathy and those who are extremely agitated need to be ventilated to allow adequate management.
- Respiratry tract infection is common in acute liver failure.

- Hypoxaemia can also result from intrapulmonary haemorrhage or adult respiratory distress syndrome; these should be managed expectantly and often require mechanical ventilation and positive end-expiratory pressure.

e. Sepsis:

- Many patients with acute liver failure succumb to sepsis .
- Frequent cultures, frequent chest X-ray and close attention to line sites are required.
- Infections are often bacterial and both gram-positive as well as gram negative organisms are important.
- Selective intestinal decontamination (oral neomycin, matronidazole or lactulose) reduces the risk of infection with gram-negative bacilli.
- Prophylactic antibiotics are not routinely used but any slightest indication of sepsis should be treated with broad spectrum antibiotics.
- Aminoglycosides should be avoided.

f. Coagulopathy:

- Patients with acute liver failure may develop haemorrhagic complications because of severe coagulation disorders caused by the lack of coagulation factors of hepatic origin.
- Prothrombin time is a very useful indicator of prognosis and therefore should not be corrected with fresh frozen plasma unless there is bleeding or before an invasive procedure; moreover, cerebral oedema may worsen with the unnecessary transfusion of blood products.
- Abnormal or low platelet concentrations are often found and consumptive coagulopathy (DIVC) is also seen.
- Acid suppresants (eg. omeprazole 40 mg od) or sucralfate (1 g qid) are given for prophylaxis against gastrointestinal bleeding

g. Electrolyte and metabolic abnormalities:

- ***Hyponatraemia*** is common.
- ***Hypokalaemia*** associated with respiratory alkalosis may be profound and requires urgent correction.
- ***Hypophosphataemia*** can occur but correction should be cautious as levels rise rapidly if renal failure develops.
- ***Hypoglycaemia*** is a hallmark of fulminant liver failure; thus blood glucose should be monitored regularly(4 – 6-hourly) and administration of 10% glucose is necessary.
- ***Hyperlactataemia and metabolic acidosis*** are found in 30% of cases and have a very poor prognosis (10% survival); correction with sodium bicarbonate infusion needs to be done carefully and dialysis may be necessary.
- ***Hypocalcaemia*** may occur (especially if acute pancreatitis occurs); 10 ml of 10% calcium gluconate daily are added to the IV infusion and another 10 ml for every unit of citrated blood transfused.

h. Nutrition:

- The catabolic rate in acute liver failure may be increased as much as four fold; thus adequate calories should be administered.
- It is accepted practice to feed enterally or parenterally patients who have grade III - IV encephalopathy after 72 hours.

II. Portal systemic encephalopathy (PSE)

- Treatment of the portal systemic encephalopathy of chronic liver disease depends on the removal of precipitating factors and on measures to alleviate the syndrome itself.
- This is aimed primarily at reducing the absorption of potentially neurotoxic material from the gastrointestinal tract, and is achieved by dietary alterations and by the use of agents that alter the nature and metabolism of the intestinal flora.

1. General measures:

- Please refer to measures instituted for acute liver failure.

2. Elimination of precipitating factors and exclusion of other causes:

- Recognition and elimination of precipitating factors is of utmost importance. Section A above lists some of the more common precipitants.
- Acute patients should have a careful history taken for medications, alcohol usage, constipation, diarrhoea, vomiting and recent protein intake.
- Actively look out for UGIH, electrolytes imbalances and sepsis.
- Evaluation of potential causes of encephalopathy other than, or in addition to , hepatic encephalopathy depends on clinical suspicion (refer to differential diagnosis).
- If benzodiazepine overdose is suspected, flumazenil should be administered.
- Thiamine (100mg IV) should be given routinely prior to glucose-containing solutions.
- CT scan and lumbar puncture should be done if intracranial lesion and meningitis are suspected respectively.

3. Specific management and management of complications:

- **Amelioration of ammonia production and absorption in the intestine:**

a ***Purgatives and enemas to empty the bowels of nitrogenous substances.***

- ***Lactulose*** is an osmotic purgative that produces an osmotic diarrhoea and alters intestinal flora, resulting in the production of acidic diarrhoea.
- Oral lactulose can be given in doses of 30ml 3 hourly until diarrhoea begins then reduce to10-30 ml 2-3 times daily to produce 2-3 soft stools

per day (Not diarrhoea). Excess usage can lead to dehydration and hypernatraemia.

- Lactulose enemas, prepared with 300 ml of lactulose added to 700ml of water, can be administered 2-4 times daily.

b Antibiotics:

- ***Neomycin*** given PO or by NG tube, 1g 4-6hrly or by retention enema, as a 1% solution (1-2g in 100-200ml of normal saline) 2-4 times daily for not more than 5 days to suppress the acitivty of bacterial flora in the intestinal tract thereby decreasing intestinal ammonia formation.
- ***Metronidazole*** orally (200-400mg 8hrly) can be given when neomycin is not available.

_ **Protein-free diet with adequate calories** (1600-2000kcal IV or via NG tube) in patients with grade III and IV encephalopathy. Example IV 20% dextrose (4 pints in 24 hours) should be given through a wide-bore cannula. Once clinical improvement occurs, protein diet than can slowly be introduced. A low-protein diet (20g / day) can be given to patients with Grade I or II encephalopathy and this amount can be increased by 10g every 3-4 days until a total protein intake of 40-60g / day is achieved. If deterioration occurs, intake is reduced to the previously tolerated level. Patients with chronic liver disease need protein and in the long term adequate nutrition needs a protein intake of at least 40g per day

- TPN solutions rich in branched-chain amino acids can be used in some patients.

_ **Correct bleeding with vitamin K (IV 10-30mg daily) or FFP** if bleeding tendency is present.

4. Long-term prevention strategies:

- Lactulose can be used to produce 2-3 soft (but not diarrhoeal) movements per day.
- Patients should get at least 2,000 calories per day to prevent wasting, with high fiber, while protein is limited to 20-50 g daily depending on clinical response.
- Vitamin supplementation should include thiamine (50mg per day), folate (5mg per day) and vitamin K (10mg per day).

_ UPPER GASTROINTESTINAL HAEMORRHAGE

A. Aetiology

• Peptic ulceration (duodenal and gastric ulcers)	50%
• Acute gastric erosions / gastroduodenitis	20%
• Oesophageal varices	5 – 10%
• Mallory-Weiss syndrome	5 – 10%
• Reflux oesophagitis	5%
• Others (gastric carcinoma, blood dyscrasias, Dieulafoy anomaly, hereditary telangiectasia)	

B. Poor prognostic factors in UGIH

- ***Age*** – below the age of 60 years mortality is low; above 80 years mortality is greater than 20%.
- ***High rate of bleeding*** – continuous haematemesis or nasogastric aspirate of blood and clots.
- The presence of ***hypotension*** (SBP < 100 mmHg) and ***postural hypotension*** on admission.

- Patient whose admission ***haemoglobin is below 8 g%.***
- The ***need for more than 4 units of blood*** to achieve circulatory stability within the ***first 24 hours*** during the initial resuscitation.
- If bleeding continues and subsequent transfusion requirements exceed 1 unit every 8 hours.
- Bleeding from gastric ulcer as compared to bleeding from duodenal ulcer; variceal bleeding also carries a poorer prognosis due to the underlying liver disease.
- ***Rebleeding*** within 2 days.
- Underlying ***comorbid conditions*** eg. heart disease, liver disease.
- Endoscopic finding of a ***visible vessel in the ulcer or ulcer > 2 cm.*** Patient with these characteristics are more likely to require surgical management.

C. Management

1. **All cases** with a recent (within 48 hours) significant gastrointestinal bleed ***should be admitted to hospital.*** Management of UGIH should be a multidisciplinary approach. Approximately 85% of patients stop bleeding spontaneously within 48 hours; the rest includes those who will require surgery, experience complications, or die.

2. **Initial assessment:**

- A brief ***history*** should be obtained from the patient or the relatives - the ***general conditions*** of the patient should be assessed quickly looking in particular for pallor, thready pulse, tachycardia (PR > 100 / min), hypotension (systolic < 100 mmHg), stigmata of chronic liver disease, features of portosystemic encephalopathy, tell-tale signs of coagulopathy, evidence of alcoholic intoxication or features of alcohol withdrawal.
- ***2 large bore IV cannulae*** (14 or 16G) should be inserted.
- ***A nasogastric tube*** should be inserted and aspiration should be done; the tube is then left behind for periodic re-aspiration to monitor any ongoing bleed.
- Keep the patient ***nil by mouth*** for endoscopy.
- Blood samples should be sent urgently for ***cross-matching, FBC, PT/PTT, blood sugar, urea, electrolytes, creatinine, liver function test;*** normally up to 4 to 6 units of whole blood need to be requested depending on the assessment of the severity of bleeding. ***ABG*** in ill patients.

3. **Acute resuscitation:**

- In hypovolaemic patients, the blood volume should be restored with ***saline or colloid,*** initially, and later ***whole blood.***
- The adequacy of volume replacement should be monitored closely with pulse rate, blood pressure, urine output (via a urinary catheter if deemed necessary), general condition of the patient and any ongoing blood loss (NG aspirate).

- CVP line insertion should be considered especially in the elderly and hypotensive patient who needs large volume transfusion.
- Anaemia (haemoglobin level) is a poor indicator of the need to transfusion as it does not develop immediately as haemodilution has not taken place.
- Coagulopathy needs to be suspected in patients with chronic liver disease and this has to be corrected with fresh frozen plasma and IV vitamin K. Platelet counts of <50,000/ul require platelets transfusion (4-8 U).

4. Diagnosis and definitive treatment:

- ***Urgent endoscopy*** (within 24 hours) should be performed to confirm the site of bleeding (which is possible in 80% of the cases).
- A bleeding peptic ulcer should be injected with adrenalin solution (or ethanol) or the vessel should be coagulated with a heater probe, electrocautery or laser therapy; if this fails to arrest the haemorrhage, surgical management needs to be instituted.
- Mallory-Weiss tear usually stops bleeding spontaneously (90%); however, endoscopic therapies as mentioned above may be useful in a still bleeding lesion. If bleeding persists, surgical repair is indicated.
- Varices can be injected with a sclerosant or banded with the endoscope (these are the treatments of choice and the success rate is over 80%)

5. Other forms of treatment for bleeding oesophageal varices:

- There are several forms of medical therapy as emergency control of bleeding whilst awaiting for endoscopy or, if the sclerotherapy fails.

a. Octreotide:

- This is a synthetic somatostatin analogue.
- It causes selective splanchnic vasoconstriction and thereby lowering the portal pressure.
- It is given as IV 50mcg bolus in the first hour followed by 25-50mcg/hr as continuous infusion for 48 hours (mix 500mcg in 50ml of NS or D5%).

b. Vasopressin:

- This is a vasoconstrictor and hence reduces portal pressure.
- It is given as 20 U slow IV bolus in 20 min followed by 0.3-0.6U/min as constant infusion for 12 hours (mix 120U in 250ml of D5%).
- It should be stopped if the patient has chest pain or abdominal colic.
- Nitrates (sublingual, transdermal or IV) should be used to reduce the complication rates and enhances its efficacy.
- It should be administered with cardiac monitoring and the success rate is 80%.
- Its complications include angina, myocardial infarction, ventricular arrhythmias, cardiac arrest, mesenteric ischaemia and infarct.

c. Balloon tamponade:

- This is used if sclerotherapy failed or is unavailable, or if vasoconstrictor therapy failed or is contraindicated eg. Sengstaken-Blakemore tube, Minnesota tube.
- It should be left in place for up to 12 hours and the success rate is up to 90%
- Complications include aspiration pneumonia, oesophageal rupture, mucosal ulceration and necrosis.

6. Additional therapies:

- Pulse rate, blood pressure, urine output, signs of rebleeding, patient`s clinical conditions, electrolytes, PT, haemoglobin and renal function need to be monitored closely.
- Patient should be managed in the ICU and good nursing care should be provided.
- Prophylactic management to prevent hepatic encephalopathy should be instituted in patient with chronic liver disease (refer to section on hepatic encephalopathy).
- Sucralfate (1g qid) should be given to reduce oesophageal ulceration following therapy with sclerosant.
- H2-antagonist (IV ranitidine 50 mg tds or IV cimetidine 200mg 6hrly) or proton pump inhibitor (omeprazole 40 mg daily) can be given to treat the underlying peptic ulcer as well as to prevent stress ulceration

7. Immediate recurrent bleeding (within 2 days):

- Repeat endoscopy to acertain the site of a rebleed and repeat the above therapeutic procedures for the specific conditions if required.
- Fluid resuscitation and blood transfusion may be required as judged by the clinical conditions of the patient.
- For peptic ulceration, recurrent bleeding often requires surgical management of the underlying ulcer.
- For recurrent variceal bleed, the following procedures may be done:
  - oesophageal transection and ligation of the feeding vessels to the bleeding varices (Sugiura procedure).
  - acute portosystemic shunt, either portocaval shunt or distal splenorenal shunt (Warren`s shunt).
  - transjugular intrahepatic portocaval shunt (TIPS).
- The underlying liver disease remains the major factor determining survival in patient with variceal haemorrhage.

8. Prevention of future recurrent haemorrhages:

- Definitive treatment of the underlying condition should be instituted.
- Malignancy should be ruled out with biopsy of any gastric ulcer.
- If test for Helicobactor pylori infection is positive in a patient with gastric or duedenal ulcer, eradication therapy should be given and acid suppresant therapy should be administered for 6 to 8 weeks to let the ulcer heal up completely.

- Repeat endoscopy should be performed in 8 weeks in the case of gastric ulcer to confirm healing.
- Risk factors of peptic ulceration and acute gastric erosion such as smoking, and NSAID abuse should be eliminated.
- Risk of recurrent variceal bleed is 60 to 80% over 2 years.
- Long term injection sclerotherapy or banding leads to obliteration of the varices by fibrous tissue (complications include ulceration, stricture, perforation, mediastinitis, etc).
- Beta-blocker with or without nitrates should be used to reduce the resting pulse rate by 25% decreases cardiac output and causes splanchnic vasoconstriction, and reduces incidence of variceal bleeding eg. propranolol 40-80mg tds.
- Surgical procedures for long term management of oesophageal varices:
  - portosystemic shunting (eg. Warren`s shunt).
  - liver transplant.

5. NEUROLOGY

_ MENINGITIS & OTHER CNS INFECTIONS

I. Meningitis

A. Causes

1. Bacteria
- Neisseria meningitidis*
- Haemophilus influenzae*
- Streptococcus pneumoniae*
- Staphylococcus aureus
- Listeria monocytogenes
- Gram-negative bacilli
- Mycobacterium tuberculosis
- Treponema pallidum

2. Viruses
- Enteroviruses
  Echo
  Coxsackie
  Polio
- Mumps
- Herpes Simplex
- HIV
- Epstein-Barr virus

3. Fungi
- Cryptococcus neoformans

Most common

B. Clinical Features

- Fever, malaise, rigors, severe headache, photophobia, nausea & vomiting. Seizures & mild changes in mental status may be present.
- Neck stiffness, Kernig's sign.
- Brudzinski 's sign - bending the head forward produces flexion movements of the lower extremity.
- Focal neurological deficits may be present as a result of complications of meningitis.
- The very old, very young & immunocompromised may have minimal symptoms and signs or have very fulminant presentations.
- Most cases of tuberculous or cryptococcal meningitis have a subacute presentation, where headache and an often ignored low grade fever predominate.

C. Investigations

- ***Lumbar puncture***: Measure opening pressure. Send for gram stain, culture, indian ink, acid fast bacilli, cell counts, protein, glucose, virus studies, latex agglutination and antigen study as indicated.

- ***CT scan or MRI*** prior to LP if ***i) Diagnosis is in doubt, ii) Increased ICP iii) Presence of focal neurological signs.*** Some neurologists prefer to have a CT scan prior to LP in all patients.
- ***Blood culture, FBC, BUSE, plasma glucose, urine culture, nose swab, VDRL.***

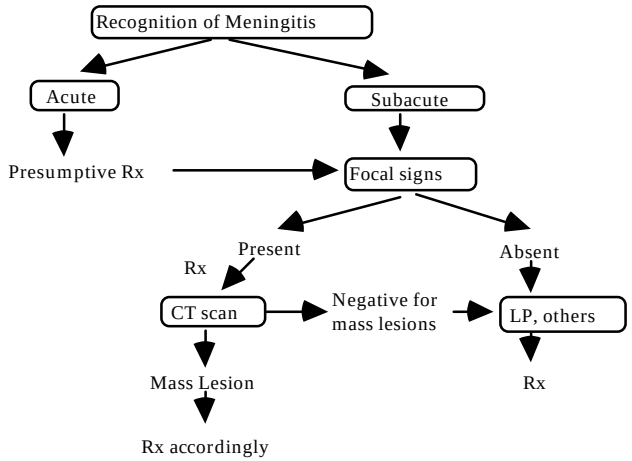
CSF Findings:

	Cells	**Cell Type**	**Glucose**	**Protein (mg/dl)**
Normal	0-5	Lymphocytes	1/2-2/3 serum	10-40
Meningitis				
-Bacterial	10-100,000	PMN	Low	Increased
-Viral	10-2,000	PMN (early) Lymph (late)	Normal	Normal to increased
-TB & Fungi	10-1,000	Lymphocytes	Low	Increased
Brain Abscess	10-500	PMN (early) Lymph (late)	Normal	Early: Increased Late: Normal
Encephalitis	10-2,000	PMN (early) Lymph (late)	Normal	Normal to increased

PMN - Polymorphonuclear cells.
Lymh - lymphocytes
CSF may be normal in early bacterial meningitis, do not hesitate to repeat LP if signs persisted
Very high cell counts eg.>50,000 suggests a ruptured brain abscess
Antibiotic therapy substantially changes the CSF pictures in pyogenic bacterial meningitis, leading to a fall in cell count, increased proportion of lymphocytes and fall in protein level. However, the low CSF glucose level usually persists.

D. Management

An algorithm for the initial strategy of management of patients with suspected bacterial meningitis:



- Send investigations before starting treatment. However, urgent empirical antibiotics need to be given prior to investigations in the moribund patient, if meningococcal meningitis is suspected and if symptoms onset is <24 hours.
- In suspected meningococcal septicaemia (young adult with purpuric rash) with hypotension, give IV hydrocortisone 200mg in case hypotension is due to adrenal infarction (Waterhouse-Frederichsen syndrome).
- If CT scan is needed prior to lumbar puncture, take blood cultures and start antibiotic therapy, then, arrange for CT scan.
- In other patients, a lumbar puncture should be done without delay.

1. Antibiotics:

_ ***When pathogen is unknown:***

Benzylpenicillin 3-4 mega IV 4hrly *or* Ampicillin 2-4g IV 6hrly
and
Chloramphenicol 1g IV 6hrly
or
Cefotaxime 2g 4-6 hrly (8-12g / day)
or
Ceftriaxone 2g 12 hrly

Special considerations:

a Post-neurosurgery or post-head trauma or shunt related:
- Cloxacillin or vancomycin + 3rd generation cephalosporin.
- Early shunt removal usually necessary in shunt related cases.

b. Immunosuppression or malignancy:

- Ampicillin / penicillin + 3rd generation cephalosporin as the commonest organisms are S. pneumoniae & gram negative bacilli. Ampicillin has the advantage of covering listeria which can also occur in these group of patients.

* *Once organism is known, use most appropriate antibiotics.*

When pathogen is known:

a. On Gram's staining:

- ***Gram positive cocci (S. pneumoniae):*** Benzylpenicillin or chloramphenicol or third generation cephalosporin
- ***Gram negative cocci (N. meningitidis):*** Benzylpenicillin or chloramphenicol or third generation cephalosporin. This treatment produces a clinical cure, and the patient might need meningococcal eradication therapy with rifampicin to render him non infectious.
- ***Gram positive bacilli (Listeria monocytogenes):*** Ampicillin plus aminoglycoside.
- ***Gram negative bacilli (H. influenza, coliforms, P aeruginosa):*** Broad spectrum cephalosporin plus aminoglycosides.

b. On culture/CSF analysis/serology:

- ***S. pneumoniae:*** Benzylpenicillin or chloramphenicol or third generation cephalosporin.
- ***N. meningitidis:*** Benzylpenicillin or chloramphenicol or third generation cephalosporin.
- ***H. influenzae:*** Chloramphenicol or third generation cephalosporin
- ***Staph. aureus:*** Cloxacillin or vancomycin.
- ***Listeria monocytogenes:*** Ampicillin and aminoglycosides.
- ***Pseudomonas aeruginosa:*** Ceftazidime plus aminoglycoside.
- ***Tuberculosis:*** Rifampicin, etambutol, isoniazid and pyrazinamide.
- ***Neurosyphilis*** *(either one):*
  - Procaine penicillin 1.8-2.4 mega IM daily+ probenecid 500mg qid for 14 days.
  - Benzylpenicillin 2-4 mega IV 4hrly + probenecid 500mg qid for 14 days.
  - Doxycycline 100mg bd for 28 / 7*.
  - Tetracycline 500 mg qid for 28 / 7*.
    **for Penicillin allergy*

Recommended antibiotic dosages:

 # Vancomycin 1g 12 hrly.
 # Ceftazidime 2g 8hrly.
 # Cloxacillin 2g 4 hrly.
 # Gentamicin, tobramycin, netilmicin 5mg/kg/day divided into 2-3 doses.
 # Amikacin 15mg/kg/day divided into 2-3 doses.

* Antibiotics are generally given for 7-14 days or until patient is afebrile for 7 days. However, the duration of therapy should be tailored to the individual patient on the basis of the clinical and microbiological response as below:

Pathogen	***Suggested duration of therapy (days)***
H. influenzae	7
N. meningitidis	7
S. pneumoniae	10-14
L. monocytogenes	14-21
Gram-negative bacilli (other than H. influenzae)	21

2. Systemic steroids:

- Limited data on dexamethaxone in adults, suggest use when CSF gram stain positive (indicates many bacteria), patient in coma, evidence of increased ICP +/- cranial nerves paralysis.
- Dexamethasone can be used at dose of either 0.4mg/kg 12 hrly IV for 2 days or 0.15mg/kg 6hrly IV for 4 days. The first dose should be given before or with the first antibiotic dose.

3. Supportive measures:

- Maintenance of airway patency and electrolyte balance.
- Attention to fluid balance. Losses are increased due to fever.
- Treat pain with paracetamol, NSAIDs , codeine or morphine.

4. Complications and their treatment:

i) Raised intracranial pressure:
- Elevate the head of the bed to 30^{o}. Steroids may be useful as discussed above.
- Mannitol should be given if there is evidence of brain shift or herniation.

ii) Hydrocephalus:
- Hydrocephalus may require an intraventricular shunt.

iii) Seizures:
- Seizures should be treated with standard therapy.

5. Prophylaxis:

- Close contacts of those with meningitis due to ***H influenzae*** (especially in children) and ***meningococcus*** (adult and children) are at high risk and prophylaxis should be given with ***rifampicin*** (600mg/12h PO for 2 days in adults) & children 10mg/kg twice daily for 2 days.
- In whom rifampicin is contraindicated, use:
  For adult, a single IM ***ceftriaxone*** 250mg or ***ciprofloxacin*** 500mg as a single oral dose.
  For children under 15, a single dose of IM ***ceftriaxone*** 125mg.

II Management of other CNS infections

1. Brain abscess:

a. Primary or contiguous source:

- Third generation cephalosporin (cefotaxime or ceftriaxone) + metronidazole 7.5mg/kg 6 hrly

or

Benzylpenicillin 20-24 mega IV daily in divided doses + metronidazole.

b. Post-surgical, post traumatic:

- Cloxacillin 2g 4hrly + third generation cephalosporin

or

- Vancomycin 1g 12 hrly + third generation cephalosporin (if MRSA is suspected)

If CT scan suggest cerebritis, abscess <2.5cm and patient is neurologically stable & conscious, start antibiotics and observe. Otherwise surgical drainage is necessary. Neurological deterioration usually mandates surgery.

2. Subdural empyema:

- Urgent neurosurgical referral should be done. Immediate surgical drainage is indicated, followed by a course of high-dose antibiotics. Choice of antibiotics is as in primary brain abscess.
- The customary duration of postoperative antibiotics is 3 weeks.

3. Viral meningoencephalitis:

- Viral meningitis is usually treated supportively. However, when there is any doubt, antibiotics as in bacterial meningitis should be given.
- ***Herpes encephalitis:*** In suspected cases (eg. CT scan or MRI showing inflammation and oedema in the inferior frontal and anterior temporal lobes, EEG with periodic sharp wave activity temporally on a background of focal or diffuse slowing, or positive CSF herpes PCR), acyclovir 10mg/kg IV 8hrly should be given for 10-14 days (reduce dose in renal failure).
- If ***cytomegalovirus infection*** is suspected (eg. in renal transplant patients or AIDS patients), gangciclovir 2.5-5.0mg/kg IV (infused over 60 mins) every 8hrly for 14-28 days depending upon response, should be given.

4. Cryptococcal meningitis:

Normal host:

- Amphotericin B IV plus flucytosine IV or orally is recommended as standard therapy. Amphotericin B can also be given alone.
- ***Amphotericin B*** 0.25mg/kg IV daily increasing to 0.7-1mg/kg over 3-4 days and is continued for 4-6 weeks, or until a minimum total dose of 1g has been given (usually 1.5-2 g). Therapy is generally continued if CSF

sugar is low. When flucytosine is used together, amphotericin B at a dose of 0.3mg/kg/d is as effective as higher doses of amphotericin B alone.

- ***Flucytosine*** if used should be given at a dose of 100-150mg/kg/day at 4 divided doses.
- ***Fluconazole*** 400mg od for 8-10 weeks can be used as an alternative for less severely ill patient.
- Some advocate amphotericin B 0.7mg/kg IV daily with flucytosine until there is marked improvement (usually 2-3 weeks), and then complete a 10 week course with fluconazole 400mg PO daily.

AIDS and other immunocompromised hosts:

a. Abnormal mental state :

- Amphotericin B 0.7-1.0mg/kg IV daily with or without flucytosine 100-150mg/kg/day until there is marked improvement (usually 2-3 weeks), and then complete a 10 week course with fluconazole 400mg PO daily.
- Alternatively: IV amphotericin 0.7-1mg/kg/day for 6-10 weeks, or until a minimum total dose of 1g and normal CSF sugar.

b. Normal mental state:

- Fluconazole: In this group of patients, fluconazole 400mg/day for 10 weeks has efficacy comparable to that of amphotericin B, (successful outcomes were lower but fluconazole was much better tolerated and with fewer adverse effects).
- Combination of fluconazole and flucytosine may be more efficacious than monotherapy.
- Itraconazole at a dose of 200mg bd may be used as in fluconazole. Efficacy is probably lower.

Maintenance treatment:

- The risk of recurrence in patients with AIDS following treatment of cryptococcal meningitis is high (>50%) without long term suppresive therapy. Therefore, maintenance treatment should be given after treatment of an acute episode in HIV-related cases.
- Fluconazole 200mg daily is the treatment of choice.
- Itraconazole 200-400mg daily may be a useful alternative.

Monitoring:

- Patients should be monitored for FBC, BUSE, renal function at least twice weekly.
- If initial lumbar puncture indicates elevated opening pressure or clinical course suggests development of raised ICP, repeated lumbar punctures may be required (+/- shunting) with repeated CT scans of the brain.

_ ***Guides for the use of Amphotericin B***

General principles:

- Parenterally.
- Test dose required (1mg in 20ml of D5%administered over 20-30 mins).
- Diluting amphotericin B in D5% to 0.1mg/ml (precipitates in saline).
- Concentrations up to 1.4mg/ml in D5% are stable in vitro and may be useful for volume-overloaded patients (this conc must be given via a central line).
- Infuse over 2-6 hrs daily.
- To determine minimum tolerated infusion duration, reduce duration of infusion by 30 mins daily (to a minimum of 2 hours) until intolerance demonstrated (fever, chills, hypotension, nausea and vomiting), then increase by 30 mins and administered further doses over this period.
- Therapy is usually initiated after test dose with a daily dose of 0.25-0.3mg/kg of body wt (in those with impaired cardio-renal function or a severe reaction to the test dose, start with smaller dose eg. 5-10mg), doses may gradually be increased by 5-10mg per day to final daily dosage of 0.5-0.7mg/kg.
- A daily doses of 1.0mg/kg/day can be given given for severe infections (as tolerated by patient).
- Doses up to 1.5mg/kg have been used for uncommon resistant infections (max).
- Since amphotericin has a serum elimination (half-life) of about 24 hours, a dosing interval of every two days is probably adequate for the treatment of less severe infections, could be used if the patient is past the acute phase of the infection.

Dosage adjustment for renal dysfunction:

- Normal dosing interval Q24 H.
- Creat Cl >60ml/min: no adjustment needed.
- Creat Cl 30-60ml/min: extend interval to Q2 days.
- Creat Cl <30ml/min: avoid drug if possible.

Side effects:

- Hypotension.
- Fever and rigors.
- Anorexia, nausea, and vomiting.
- Anaemia.
- Hypokalaemia.
- Nephrotoxicity.
- Phlebitis.
- Pulmonary reactions (acute dyspnoea, hypoxaemia, interstitial infiltrates).

Monitoring:

- Monitor BP prior to and at 5 mins, 15 mins, and 30 mins during infusion on days 1, 2, 3 and continue during subsequent infusions until no changes in blood pressures are observed with the infusion.
- Monitor K conc, Hb, serum creatinine at least twice weekly.

_ COMA

A. Causes

a. Trauma
b. Post-ictal
c. Drugs & alcohol- eg. morphine, hypnotics, alcohol, organophosphates, paraquat
d. Vascular:
- Cerebral haemorrhage
- Subarachnoid haemorrhage
- Cerebral infarction
- Extradural & subdural haematoma
- Hypertensive encephalopathy

e. Cerebral tumours
f. Cerebral Infections:
- Meningitis
- Encephalitis
- Abscess
- Cerebral malaria

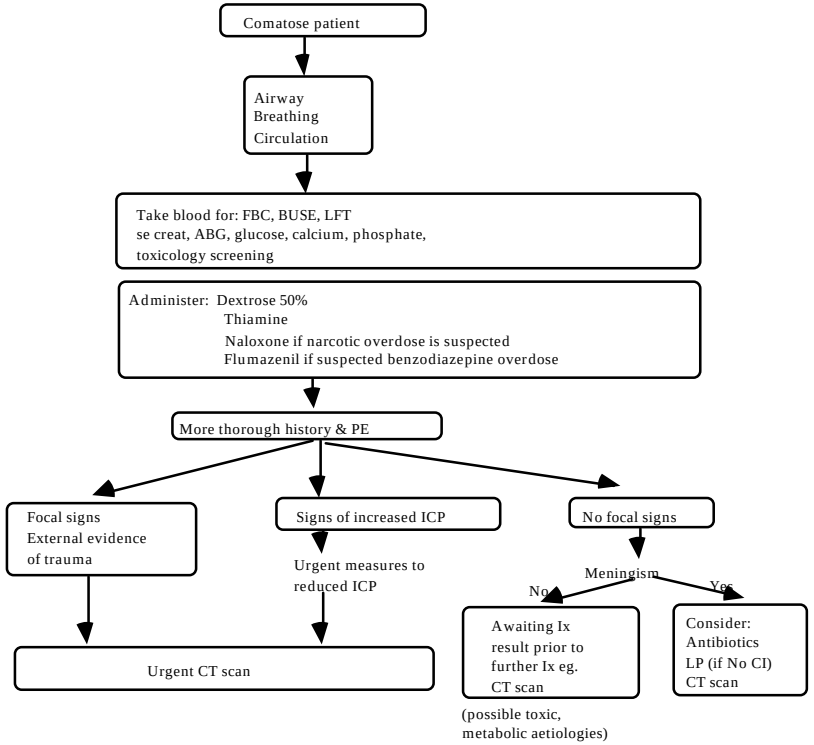
g. Global anoxia-ischaemia (fat emboli, cardiopulmonary arrest, strangulation, exsanguination).
h. Metabolic causes:
- Uraemia
- Diabetic emergencies:
  Hypoglycaemia
  Hyperglycaemic non-ketotic coma
  Ketoacidosis
- Endocrine:
  Myxoedema
  Acute hypocortisolism
- Respiratory failure (Hypercapnia)
- Hypothermia/Hyperthermia
- Hyponatraemia/Hypernatraemia
- Hepatic encephalopathy
- Metabolic acidosis
- Hypercalcaemia/Hypocalcaemia
- Thiamine deficiency (Wernicke's encephalopathy).

i. Psychogenic coma.

B. Assessment

- Coma requires prompt institution of basic critical care to prevent ongoing neurological injury.
- Rapid recognition & treatment of remediable causes of coma can restore neurological function.
- Measures to stabilize patients should be started as soon as possible after initial assessment & take precedence over more detailed physical examination and investigations.

- Algorithm for the approach to a comatose patient:



I. History

- A history should be obtained from accompanying relatives, friends, ambulance drivers or the police. Find out whether they have diabetes

mellitus, epilepsy, hypoadrenalism, history of injury, taking corticosteroids, etc.

II. Examination

1. Examination should commence with assessment of the **cardiac and respiratory status.** Only once the airway and cardiac output are satisfactory should further physical and neurological examination commence.
   - ***a. Airway.***
   - ***b. Breathing, look for:***
   - Cheyne-stoke breathing (Bilateral cerebral dysfunction, acute heart failure, uraemia, CO2 retention).
   - Kussmaul breathing (diabetic ketoacidosis, uraemia).
   - Ataxic respiration (medullary respiratory centre damaged).
   - ***c. Circulation:***
   - BP, Pulse.
   - ***d. Temperature*** (Hypothermia or hyperthermia should be looked for).

2. **Level of consciousness (Glasgow coma scale):**
   - ***a. Best motor response***
     - 6 Obeys commands
     - 5 Localizes pain
     - 4 Withdraws to pain
     - 3 Abnormal flexion
     - 2 Abnormal extension
     - 1 No movement
   - ***b. Best verbal response***
     - 5 Orientated and appropriate
     - 4 Confused conversation / Disorientated
     - 3 Inappropriate words
     - 2 Incomprehensible sounds
     - 1 No sounds
   - ***c. Eye-opening***
     - 4 Spontaneous
     - 3 To speech
     - 2 To pain
     - 1 No eye opening
   - # *To assess the motor response, ask the patient to move the limb. If there is no response, apply firm pressure to the nailbed. Test and record for each of the limbs. Test for a localizing response by pressure on the supra-orbital notch or sternal rub. For the purpose of assessment of conscious level, the best motor response is taken.*
   - # *The GCS is a valuable tool in predicting likely outcome from coma, but it has limitations and should not be the only factor used to assess prognosis. The cause of coma is also an important predictor. Patients with GCS 3-8 generally have far worse prognosis than those with >8.*

3. **Head and face, look for:**
   - Injuries.
   - Facial asymmetry (7th nerve palsy).

4. **Eyes:**
   a. Pupils, look for:
   - Pin point pupils (pontine lesion, narcotic poisoning, organophosphate poisoning).
   - Midposition fixed pupils (4-6mm) (midbrain lesion).
   - Unilateral fixed dilated pupil (uncul herniation with 3rd nerve compression).
   - Bilateral fixed dilated pupils (brain death, deep coma of any cause).
   - Skew deviation (brain stem lesion).

   b. Eye position:
   - Absence of Doll's eye reflex (brain stem lesions, deep coma).
   - Sustained conjugate lateral gaze towards one side (destructive hemisphere lesion of the same side, pontine brain stem lesion of opposite side, irritative frontal lesion of opposite side).
   - Dysconjugate gaze (3rd or 6th nerves palsy).

   c. Corneal reflex.

   d. Fundus:
   - Papilloedema (increased ICP).
   - Retinal haemorrhage (subarachnoid haemorrhage).

5. **Ears & nostrils:**
   - Look for bleeding, middle ear discharge or drum perforation or CSF leak.

6. **Tongue and mouth:**
   a. Localized injury.

   b. Breath:
   - Alcohol (alcohol intoxication).
   - Ketone (Diabetic ketoacidosis).
   - Uraemic (Uraemic encephalopathy).
   - Hepatic (Hepatic encephalopathy).

   c. Gag reflex.

7. **Neck & meningism:**
   a. Neck stiffness (subarachnoid haemorrhage, meningitis, tonsillar herniation).

   b. Kernig's sign.

8. **Upper and lower limbs:**
   a. Posture:
   - Decerebrate posture.
   - Decorticate posture.

b. ***Involuntary movement.***
c. ***Tone.***
d. ***Reflexes.***
e. ***Power.***
f. ***Sensation.***

9. Body:
a. ***Signs of trauma.***
b. ***Heart*** for murmur or arrhythmia especially AF**.**
c. ***Lung*** for possible aspiration or collapse**.**
d. ***Abdomen*** for stigmata of liver disease, gastroparesis**.**

C. Investigations

- FBC, BUSE, glucose, Ca, LFT, blood C&S, se T4, se cortisol, BFMP, urine ketone, plasma osmolality, CXR, ECG, ABG, toxicology, lumbar puncture (if meningitis is suspected and if no sign of increased ICP) and CT scan / MRI. Gastric lavage if poisoning is suspected.

D. Management

1. Ensure ***adequate ventilation, circulation, and body temperature.***

2. If alcohol intoxication is suspected, give ***thiamine,*** 100mg IV or IM (before giving dextrose), followed by 100mg IM or orally for 3 days.

3. If narcotic overdose is suspected (eg when pupils are pinpoint, respiratory rate is <10 / min), ***naloxone hydrochloride***, 0.4-1.2 mg IV should be given. The dose can be repeated several times until the respiratory rate is around 15 / min (max 10mg). With opiate intoxication, response should be seen within minutes. If there is a response, start IV infusion: add 2mg to 500ml dextrose 5% or saline (4ug / ml), start at 100ml / hr and titrate against the respiratory rate and conscious level.

4. When blood glucose is low (eg. < 50 mg / dL) or when level is not obtainable, 50ml of ***50% Dextrose*** IV should be given.

5. If coma is a complication of the therapeutic use of benzodiazepine in hospital, ***flumazenil*** (a selective benzodiazepine antagonist) may be given (200mcg IV over 15s; if needed, further doses of 100mcg can be given at 1 min interval up to a total dose of 1-2 mg). Flumazenil should not be given to other patients because of the risk of precipitating fits if there is mixed poisoning with benzodiazepines and tricyclics.

6. Treat ***increased intracranial pressure.***
- The comatose patient should be intubated to protect the airway & maintain hyperventilation when elevated ICP is suspected.
- For further measures refer to section on intracranial hypertension.

7. Control ***seizures*** (see section on seizures).

8. Treat the ***underlying problem*** eg. antibiotics for meningitis.

9. ***General care*** of comatose patient:

- Hydration and nutrition - maintained with IV fluids or by NG feeding. N.B. Presence of gag reflex is no gurantee against aspiration in a patient with changes in sensorium
- Cutaneous pressure sores - 2hourly turning of patient.
- Joint mobility- maintained with passive exercise.
- Corneal abrasions - can be prevented by taping the eyelids closed after applying methylcellulose drops (1 drop every 4 hourly).
- Indwelling urinary catheters or condom catheters in man.
- Prevention of gastric stress ulceration with sucralfate, H2 antagonists or proton pump inhibitors.
- Heparin SC 5000U 12hourly, should be given to prevent DVT.

_ CEREBROVASCULAR ACCIDENT (STROKE)

Stroke Manifestations:

1. ***Cerebral Infarction***
   a. Thrombosis
   b. Embolism

2. ***Spontaneous intracranial haemorrhage***
   a. Intracerebral haemorrhage
   b. Subarachnoid haemorrhage

I. Cerebral Infarction (Ischaemic stroke)

- Refers to occlusion of a cerebral blood vessel in association with an inadequate collateral circulation. Can be due to cerebral thrombosis or cerebral embolism.
- Aetiology:
  (a) ***Cerebral thrombosis***: Atherosclerosis, hypertension, arteritis, arterial dissection, aortic arch syndromes, syphilis, angiography, infection, and haematological disorders.
  (b) ***Cerebral embolism:*** Left atrial thrombus associated with mitral stenosis or AF, a mural thrombosis following MI, or bacterial endocarditis.
- Risk factors:
  Hypertension, DM, obesity, heart disease, family history, cigarette smoking, hyperlipidaemia, OCP, alcohol and age.

A. Clinical Presentation

1. ***Cerebral Thrombosis***
   Commonly preceded by TIA. Generally no headache. Neurological deficit may come on suddenly or gradually progresses to its full extent over a matter of hours. The symptoms and signs are dependent on the size of the lesion and the artery that is affected.
2. ***Cerebral Embolism***
   Characterized by its sudden onset and the rapid development of complete neurological deficit. The neurological deficit is dependent on the artery involved.

B. Investigations

- ***FBC, ESR, BUSE, RBS, UFEME, se cholesterol, triglycerides, VDRL, coagulation profile, ECG, & CXR*** should be done in all patients. ***ABG*** should be done if hypoxia is suspected.
- ***CT scan*** should be done for most patients. When to scan is controversial, but it is reasonable to perform scanning at 1-2 days as infarction may not be seen on a non-contrast CT within the first 24 hours.
- ***Urgent CT scanning*** should be performed if:
  - diagnosis is unclear.
  - signs of raised ICP and / or brain shift are present.
  - intracerebral haemorrhage or subarachnoid haemorrhage is suspected.
  - a cerebellar stroke is likely.
  - anticoagulation or thrombolytic therapy is contemplated.
- ***CSF examination*** - may be indicated if a subarachnoid haemorrhage is to be excluded and CT scan is not available or when infection, multiple sclerosis or neurosyphilis are suspected.
- ***ANF, anticardiolipin antibody, lupus anticoagulant, PT, aPTT, protein C, S, antithrombin III, homocystine level or other specific tests*** may be required in young patients without common risk factors.
- ***Echocardiography*** should be done if cardiac embolism is suspected.
- ***Carotid doppler studies*** should be performed in patients who would be suitable for carotid endarterectomy (patients with minor ischaemic stroke & patients with a more substantial stroke who have a good recovery who are otherwise medically fit) in anterior circulation infarct.

C. Management

¥ Acute therapy

1. General measures:

a. Coma nursing, physiotherapy, maintainence of electrolytes and glucose within normal ranges, maintenance of fluid balance, treatment of associated illnesses, etc.

- Hyperglycaemia and increased body temperature have both been convincingly associated with a bad stroke outcome and both require adequate therapeutic measures.
- Avoid flat supine position; elevate head of bed 15-30 degrees.
- Dehydration may increase morbidity and mortality in patients recovering from acute stroke and elevated serum osmolarities should be avoided.
- The use of hypotonic saline should be avoided when rehydrating stroke patients, as the added free water in hypotonic IV solutions may produce a relative plasma hypoosmolarity that can cause a subsequent shift of fluid into the brain. Use normal saline.
- The use of hyperglycaemic solutions in patients with acute stroke should be avoided.
- Most patients require 2,000 to 2,500ml fluid per 24 hours.
- Patient who are unconscious and not able to sit upright should be kept nil by mouth. Otherwise, the swallowing ability can be assessed by

giving one teaspoon of water increasing to second teaspoon of water and then half a glass of water if tolerating. Patients who cannot tolerate fluid (eg. no attempt to swallow, water leaks straight out, coughing, choking, wet/gurgly voice after drinking) should be kept nil by mouth or feeding by NG tube and reassess again later.

b. Oxygen:

- Supplemental oxygen is important to prevent hypoxaemia.

c. Blood pressure control:

- Lowering of blood pressure should be avoided in the first 10 days unless it is critically high.
- Severe hypertension (>200/>120mmHg) should be treated; but it is important to reduce the blood pressure slowly (to about 100-110mmHg diastolic & 160-180 mmHg systolic) in order to prevent the development of further cerebral ischaemia due to hypotension. Further reduction to more normotensive levels can be achieved more slowly during the ensuing 2-3 days.
- Antihypertensive agents can be given orally or intravenously. Beta blockers or labetolol are drugs of choice for BP control.
- If hypotension is present, it should be corrected.

d. Treatment of cerebral oedema:

- Maximum in 24-72 hours.
- Steroids are not effective in strokes. Mannitol and frusemide may be helpful. Other measures include 30^{o} head tilt, hyperventilation (target PCO2 25-30 mmHg). In younger patients with large, space occupying, right-sided MCA territory or cerebellar infarctions, craniectomy can be done when conservative therapy fails (see section on intracranial hypertension).

2. Antiplatelets:

- When initiated early in hospitalized patients, aspirin therapy produces a small but significant benefit within weeks of onset of stroke.
- Unless there are clear contraindications (eg. aspirin hypersentivity, active peptic ulcer disease, recent GI bleeding or if the patient is already taking an anticoagulant), immediate use of aspirin (with an initial dose of about 150-300mg daily, though a lower maintenance dose might suffice) should be considered in all patients with acute ischaemic stroke, especially if a CT has excluded intracerebral haemorrhage.

3 Anticoagulation:

- ***Unfractionated heparin*** and ***low molecular weight (LMW) heparin*** have little overall effect in preventing early recurrent stroke; any reduction in ischaemic stroke is offset by an increase in haemorrhagic stroke.
- ***Anticoagulation with unfractionated heparin*** may be indicated for :
  (i) Progressing strokes.
  (ii) Cardiogenic emboli eg AF - delay of several days may be required (see below).

(iii) TIAs particularly recent or crescendo TIAs and/or tight stenoses of the carotid or vertebrobasilar systems.

- Intracranial-haemorrhage and non-ischaemic causes of stroke must be excluded before anticoagulation is started.
- If a cardiac source for emboli is identified, full anticoagulation should be delayed for a few days (2-3 days) after a small or moderate ischaemic stroke and for one to two weeks if there is a large infarction.
- In patients who are on warfarin and with CVA, warfarin should be discontinued; if there is no evidence of intracerebral haemorrhage or haemorrhagic infarction, it can be resumed 72 hours later.

4. Thrombolytic therapy:

- rtPA may be safe and effective within 3 hrs but not after 4 hours of symptom onset.
- Risk of bleeding is high, so careful evaluation of imaging study is required.
- The FDA has approved the use of IV rtPA to treat acute stroke within 3 hours of symptom onset.
- Close attention to issues of patient eligibility and acute medical management are critical because of the potential for serious complications in otherwise unselected cases.

Special considerations:

1. Stroke in evolution:

- Rule out hemorrhage with CT Scan.
- Acute anticoagulation therapy or thrombolysis should be considered.

2. Cerebellar Involvement:

- May present with ataxia, loss of coordination, increased drowsiness.
- In patients with change in mental status, consider increased oedema or cerebral haemorrhage.
- Compression on 4th ventricle leads to CSF Outflow Obstruction and elevated ICP.
- May progress rapidly to death (urgent CT scan essential), surgical decompression of posterior fossa may be needed.

¥ Stroke (Primary and secondary) prevention

1. Routine interventions:

- ***Blood pressure*** normalization.
- ***Stop smoking.***
- ***Obesity*** - weight reduction will improve cardiovascular status and glucose tolerance.
- ***Diabetes Mellitus*** - good control is essential.

- ***Cholesterol*** - Use of stastin to reduce cholesterol level has been shown to reduce incidence of stroke.
- Improvement in physical activity.
- Hormone Replacement Therapy (HRT) may reduce risk slightly.

2. Antiplatelet agents:

- Antiplatelet therapy causes significant risk reduction for stroke, myocardial infarction or vascular death in the whole population at risk and in patients with cerebrovascular diseases.
- For all patients having experienced a prior TIA / stroke, ***Aspirin*** is the agent of choice because of its antiplatelet activity, low cost, and efficacy. Dosage: 75-300mg / day.
- ***Ticlopidine*** 250mg bd is an alternative to aspirin in patients who cannot tolerate or who have failed on aspirin therapy. Although ticlopidine was shown to be slightly more effective than aspirin, ticlopidine has a higher incidence of adverse effects (diarrhea, rash, and severe neutropenia). FBC should be monitored in 2 weeks and 1 month.
- The ***combination of antiplatelet agents*** with different mechanisms of action may have additive effects in preventing stroke recurrence eg. aspirin 75-300mg daily + dipyridamole 75mg tds or SR 400mg daily.
- If TIAs / stroke continue to occur on aspirin, options (after extensive search for treatable risk factors) are:
  - Consider other antiplatelet therapies eg. ticlopidine, clopidrogrel.
  - Add dipyridamole or combination of aspirin with other antipletelet agents.
  - Consider anticoagulation.

3. Anticoagulation:

a. Atrial fibrillation:

- Anticoagulation is recommended for all patients with chronic or paroxysmal atrial fibrillation if cardiac disease such as ***hypertension, rheumatic heart disease, coronary artery disease, CCF, or thyrotoxicosis is present*** (in the absence of ***contraindication*** eg. coagulation disorder, GI bleeding, liver disease, frequent falling). Lone AF in patients age > 65 can be treated with either aspirin or anticoagulation (refer to section on AF for details).
- Short-term anticoagulation prior to attempting to convert (electrically or pharmacologically) to sinus rhythm should be considered for patients who have been in AF or flutter for longer than 2 days.

b. Heart valves:

- All patients with mechanical prosthetic cardiac valves should receive anticoagulant.

c. Others:

- Warfarin can also be used if a patient has had several TIAs that were not controlled by aspirin.
- If TIAs / stroke continue to occur on anticoagulation, options (after extensive search for treatable risk factors) are:
  - Increase the INR range.

- Add antiplatelet agents.

4. Carotid Endarterectomy

- All patients with transient ischaemic attacks or recent minor strokes without an obvious cardiac cause, who are otherwise fit for surgery, should be screened with noninvasive ultrasonographic techniques.
- Those with minimal narrowing or none should be treated with what is currently the best medical care.
- Those with moderate or severe narrowing should be seriously considered for arteriography.
- Patients with high-grade stenosis (70-99%) from arteriography should be considered for carotid endarterectomy.
- Perioperative risks are increased in female pateints, patients with peripheral vascular disease and systolic hypertension (>180 mmHg).

II. Intracerebral Haemorrhage

A. Causes

- Hypertension, arteriovenous malformations, cerebral tumours, haematological disease, berry aneurysms, mycotic aneurysms and etc.

B. Clinical Features

- Often indistinguishable from cerebral infarction.
- Severe headache, vomiting and impairment of consciousness are more common with haemorrhage. Neurological deficit is of sudden onset.

C. Investigations

- CT scan is required to determine the exact site and size of the haematoma and exclude other pathologies.

D. Management

- General measures, blood pressure control, treatment of cerebral oedema as in cerebral infarction.
- Anticoagulation is contraindicated.
- Correction of any coagulation disorders.
- Surgical evacuation of haematoma may be indicated in cerebellar haematomas and surgically accessible cerebral haematomas causing significant mass effect.
- In non-hypertensive ICH, patients should be investigated for the underlying cause (eg cerebral angiography).

III. Subarachnoid Haemorrhage

- Refers to bleeding which occurs principally within the subarachnoid space.
- Causes are rupture of an intracranial (usually Berry) aneurysm (75%), bleeding from an arteriovenous malformation (AVM) (5%), and unknown (20%).
- Rare associations with SAH:
  Bleeding disorders, mycotic aneurysms, bacterial meningitis, brain tumour, arteritis, Marfan's syndrome, Ehlers-Danlos syndrome, coarctation of aorta, polycystic kidney.

A. Clinical Features

- Sudden onset of severe headache, loss of consciousness, meningism ie. neck stiffness, Kernig's sign, photophobia, vomiting, retinal haemorrhage (subhyaloid haemorrhages), seizures, ECG abnormalities (eg.T wave inversion, ST segment changes, U waves and QT prolongation).
- Neurological deficits, related to the site of the aneurysm and size of the haemorrhage.
- Complications of SAH include rebleeding (20% at 2 weeks), vasospasm with ischaemia (day 4-14), hydrocephalus, seizures, and SIADH.

Clinical Grading system:

1. Hunt and Hess:

Grade I	Awake, with no symptoms, or mild headache and / or nuchal rigidity.
Grade II	Awake, with moderate to severe headache, and with nuchal rigidity.
Grade III	Drowsy or confused, with or without focal deficits.
Grade IV	Stuporous, with moderate to severe hemiparesis, and signs of increased intracranial pressure.
Grade V	Comatose with signs of severe increased intracranial pressure.

2. World Federation of Neurologic Surgeons (WFNS):

	GCS		*Focal deficit*
Grade I	15		Absent
Grade II	14-13	Absent	
Grade III	14-13	Present	
Grade IV	12-7		Present or absent
Grade V	6-3		Present or absent

Grade I or II patients have the best prognosis and should undergo early cerebral angiography and definitive intervention, particularly if evaluation is within the first 48 hours of onset.
Grade III patients may undergo angiography early, but then should be managed conservatively until their grade improves and surgical risk decreases.
Grade IV and V patients have a poor prognosis and require medical management until their state improves. Angiography may be performed later in such cases if they improve sufficiently to warrant more definitive care.

B. Investigations

- ***General investigations*** as in cerebral infarction.
- ***CT scan/MRI.***
- ***Lumbar puncture*** - should be performed when the clinical impression of SAH is not confirmed by CT. It is important to exclude a traumatic spinal tap (when haemorrhagic CSF is obtained, the following measures may differentiate between SAH and traumatic tap: (i) Immediate centrifugation which shows Xanthochromatic supernatant indicates SAH (ii) Comparison of the first and last specimens of CSF will show significant decline in RBC count when the blood is from traumatic tap).
- ***Angiography*** is needed if surgery is comtemplated.

C. Management

1. Initial management:

a. General care:
- Bed rest with room darkened and noise minimized.
- Sedation with phenobarbitone or diazepam is instituted to prevent excitement and elevation of BP.
- Oxygen, prevention of gastric erosions, maintenance of fluid and electrolyte balance.
- Nausea and vomiting should be treated promptly.
- Stool softeners should be given.

b. Blood pressure control:
- With the exception of patients with cerebral vasospasm, severe hypertension (diastolic >120mmHg) should be controlled with sedation, analgesias and antihypertensives. Hypotension should be avoided.
- Calcium channel blockers may have potential advantages with reference to vasospasm.

c. Prevention of vasospasm:

- ***Nimodipine*** has been shown to reduce morbidity & mortality following SAH. Nimodipine (usually given once the diagnosis is established) can be given at a dose of 30-60mg PO 4 hrly for 3 weeks initiated within 4 days of presentations. If the patient cannot take the medication by mouth, it is administered by NG tube or intravenously.
- If IV nimodipine is available, it should be given as infusion solution for 5-14 days followed by oral nimodipine for additional 7 days. Nimodipine infusion should be started at a dose of 1mg/hr for 2 hrs. If this is well tolerated and no marked reduction in blood pressure, the dose is increased after 2 hrs to 2mg/hr. Patients whose body weight is appreciably <70 kg or who have labile blood pressure should be started with a dose of 0.5mg/hr. Nimodipine infusion solution should be administered as a continuous IV infusion via a 3-way stopcock together with about 40ml/hr of D5%or NS through (not to be added toinfusion container) a central catheter using an infusion pump.

2. Definitive treatment:

a. Surgery:
- Patients who undergo surgery for ruptured aneurysms generally fare better than those who are treated medically because of the reduction in the incidence of rebleeding with surgery.
- ***Contraindications*** - surgery is not usually performed on patients in coma or with severe neurological deficits (Class IV or V) because of the high mortality and low potential for recovery.
- ***Procedures*** - Various procedures have been used and the most common of which is clipping the neck of the aneurysm.
- ***Timing*** - Early aneurysm surgery in the first 24-48 hours for patients not neurologically severely impaired is generally preferred.

b. Endovascular occlusive procedures:
- Embolization with platinum coils has been shown to be effective in patients in whom aneurysm surgery is contraindicated or with surgically unclippable aneurysms.

3. Treatment of complications of SAH:

a. Vasospasm:
- Vasospasm may be responsible for drowsiness or focal neurological signs, but these signs usually do not occur until 2-3 days after the initial haemorrhage and peak in occurrence at about 7 days.
- Transcranial doppler or cerebral angiogram may be useful to confirm cerebral vasospasm.
- Discontinue nimodipine, and antihypertensive therapy.
- Most consistently effective treatment for vasospasm remains ***hypervolaemia*** and/or ***induced arterial hypertension.*** Hypervolaemic volume expansion is accomplished by administering 5% albumin or artificial colloids. The

therapy is monitored via a central venous catheter, adjusting the central venous pressure to 8-12 cm H2O or the pulmonary capillary wedge pressure to 12-16 cm H2O. If spasm is still a problem even after hypervolemia, the BP can be raised with hypertensive agents such as IV dopamine, dobutamine etc (to keep at mean arterial pressure of 110mm Hg).

b. Rebleeding:

- Rebleeding may be immediately fatal or lead to deteriorating conscious level with apnoea.
- Ventilatory supports should be provided for the latter. If these patients improve, emergency aneurysm clipping should be considered as they are at high risk of further bleed.

c. Hydrocephalus:

- Hydrocephalus of acute onset, associated with a clinical deterioration or in severe cases warrants a ventriculostomy.

d. Cerebral oedema:

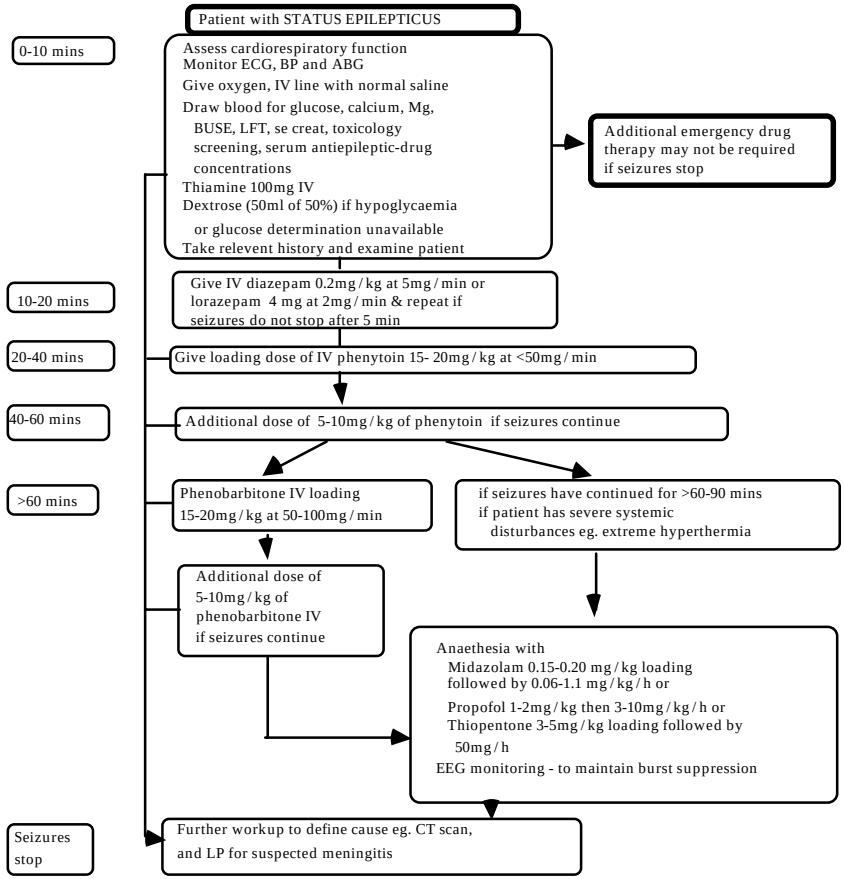
- See section on intracranial hypertension.

_ STATUS EPILEPTICUS

- Defined as repeated seizures without recovery between attacks or one single prolonged seizure lasting more than 20-30min. However, it is important to note that therapy for status epilepticus needs to begin well before 20 mins have elapsed.
- May occur with any pathology though more common in patient with space occupying lesion (esp frontal lobe), encephalitis, following head injury, when drug therapy is changed (esp. abrupt withdrawal of anticonvulsant).
- Prompt treatment is needed to reduce cerebral damage and metabolic complications (hypoglycaemia, lactic acidosis and hyperpyrexia) and prevent mortality.

A Management

Algorithm for the treatment of status epilepticus:



1. General measures:

- Maintain airway with oropharyngeal airway. Put patients on their side in a semiprone position.
- Give oxygen.
- Monitor vital signs and temperature and institute appropriate measures.
- IV infusion eg. normal saline as appropriate.
- Monitor electrolytes and acid base balance and treat cerebral oedema as appropriate. Dextrose should be given if hypoglycaemia is suspected. Thiamine should also be given if alcoholism appears likely.
- Patient should be transferred to ICU if fits persisted despite initial treatment with diazepam and phenytoin.
- Attempt should be made to identify aetiology.

2. Specific measures:

a. ***Diazepam*** - IV 0.2mg/kg at 5mg/min (usually 5-10mg), repeated after 5mins as necessary up to 20mg bolus or when seizures stop or when significant respiratory depression occurs. Following then, if seizures recur, 5-10mg IV can be given every 20-30 mins. Maximum dose is 3mg/kg/day. Diazepam can also be given rectally if IV access is not readily available. Do not give IM diazepam.

- Alternatively, ***lorazepam*** , 2-4mg IV every 5-10 mins, up to a total dose of 10mg can be given (Advantage: lower risk of hypotension and respiratory arrest, longer action, rate of injection not critical. Disadvantage: risk of acute tolerance, no effect if repeated use).

b. ***Phenytoin IV:***

- 2nd line drug if seizures persisted after 20-30 mins.
- Drug of choice due to its high efficacy, long duration of action, and low incidence of serious complications.
- Recommended ***initial loading dose***: IV 15-20mg/kg at a rate of < 50mg/min. Phenytoin should be administered manually close to the vein via a large-bore IV infusing glucose-free saline to prevent precipitation in the line. Additional IV phenytoin loading of 5-10mg/kg may need to be given in some patients (max 30mg/kg).
- Daily ***maintenance dose*** - 5mg/kg/day orally or IV 12-24 hours after loading dose.
- Continuous ECG monitoring is required. Phenytoin is ***contraindicated*** in heart block.
- Plasma phenytoin level monitoring may be required (draw blood 2-4 hours after loading dose).

c. ***Phenobarbitone:***

- An alternative for phenytoin or when seizures recur despite a full loading dose of phenytoin (Advantages over phenytoin: Quicker injection time, prolonged action, single IV line, potential cerebro-protective action).
- Usual ***loading dose*** - IV 15-20 mg/kg at a rate of 50-100 mg/min. An additional loading dose of 5-10mg/kg may need to be given in some patients.
- Daily ***maintenance dose*** - 5mg/kg/day given orally or IV 12-24 hours after loading dose.
- ECG and BP monitoring is required.

d. ***Other anticonvulsants*** which may be used include IM paraldehyde, IV lignocaine and IV sodium vaproate if facilities for immediate ventilation are not available after the above measures have been taken.

- ***Sodium valproate*** IV appears to stop some types of status epilepticus. It can be given at a loading dose of IV 15mg/kg followed by maintenance 1mg/kg/hr given 30 mins after bolus & maintained for 5-6 hrs.
- ***Paraldehyde*** (5-10ml IM) requires glass syringes as it corrodes rubber & plastic.
- ***Lignocaine*** can be given at a loading dose of 100mg (1.5-2mg/kg) IV followed by continuous infusion at 1-2mg/min.

e. In ***resistant cases***, paralysis and I.P.P.V. may be required. Midazolam, propofol or thiopentone can be given for 24-48 hours to achieve EEG burst suppression if seizures continue to occur.

_ INTRACRANIAL HYPERTENSION

A. Symptoms and Signs

1. General features:

- Headache, vomiting, papilloedema, change of conscious level.
- Hypertension, bradycardia (Cushing's reflex).

2. Herniation:

a. Diencephalic herniation (Central tentorial herniation)

- Cause by a midline lesion or diffuse swelling of the cerebral hemispheres results in a vertical displacement of the midbrain and diencephalon through the tentorial hiatus.
- (i) deterioration of conscious level (ii) small pupils and subsequently become dilated (iii) upward gaze palsy (iv) Cheyne-stokes respiration.

b. Uncal herniation (Lateral tentorial herniation)

- Caused by a unilateral expanding mass causing tentorial (uncul) herniation as the medial edge of the temporal lobe herniates through the tentorial hiatus.

- (i) deterioration of conscious level (ii) dilated, unreactive pupil ipsilateral to the mass [3rd nerve palsy] (iii) hemiparesis on either side [false localising sign- produce weakness on the same side].

c. Tonsillar herniation.

- Caused by a subtentorial expanding mass causing herniation of the cerebellar tonsils through the foramen magnum.
- (i) depression of conscious level (ii) repiratory irregularities or apnoea (iii) neck stiffness and head tilt.

B. Management

- Neurosurgical intervention is the definitive treatment for some focal causes and medical treatment is helpful for increased ICP following ischaemic, anoxic or metabolic brain necrosis.

1. General measures:

- Patient should be placed in bed with the head elevated 30 degrees and in the midline. Stimulation by family and staff (eg turning the head, suctioning) should be kept to a minimum.
- Avoid hypotonic IV solutions or fluids that contain large amounts of free water (eg 5%D / W).
- Restrict fluid to 1000ml of normal saline / m2 body surface per day and monitor BP, serum osmolality and urine output.

2. Osmotic agents:

- This can be initiated with mannitol, glycerol or other agents.
- ***Mannitol*** given in 0.5-1.0 g / kg (eg. 100-200ml of 20% over 15-30 min) every 6 hourly for 24-72 hours.
- It draws water from the brain tissue compartment into the systemic vascular compartment. The effect starts within minutes and lasts for several hours.
- The effect on both urine output and ICP is extended with a loop diuretic. IV ***frusemide*** 40-80 mg 6hourly may be given.
- Indwelling bladder catheter is necessary. Monitor vital signs, electrolytes, BU and osmolality (aim at 300-320mOsm / liter) frequently.
- Usually used in anticipation of more definitive treatment.
- If the ICP is stabilized with continuous hyperosmolar therapy, this treatment is best withdrawn slowly and with close neurological observation.
- Complications included (i) rebound increase in ICP (ii) acute intravascular volume expansion with pulmonary oedema or congestive cardiac failure (iii) dehydration and hypernatraemia.

3. Hyperventilation:

- Produces a fall in arterial PCO2 thereby reducing cerebral blood flow.
- Hyperventilation is an excellent acute treatment, but the effect on ICP is not well-sustained.
- Patient should be sedated, paralysed and ventilated.
- Maintained PaCO2 at 25-30mm Hg.

- After ICP has been controlled, a stabilizing treatment and a long-term definitive plan should be developed. Usually the first-order stablizing treatment is an osmotic treatment; with effective initiation of this osmotic treatment hyperventilation can be withdrawn.
- Withdrawal is best accomplished over 24h in approximately 5 mmHg $PaCO_2$ increments between 25-40mmHg. This time period should be longer if tachyphylaxis has developed.

4. Corticosteroids:

- Effective in reducing the oedema surrounding a tumour or an abscess (vasogenic cerebral oedema) . Ischaemic and traumatic causes of oedema (cytotoxic cerebral oedema- that associated with anoxia) are not likely to benefit from corticosteroids.
- IV ***dexamathasone*** 8mg given initially, followed by 4-8mg IV or orally 6-8 hourly. The regimen is then tapered or increased depending on patient response.
- The effect begins in 4-6 hours and peaks at 24 hours.

5. Barbiturate coma:

- When other methods of controlling increased intracranial pressure fail, IV barbiturates may be used to control increased intracranial pressure.
- Pentobarbitone, thiopentone and occasionally, phenobarbitone have been used.

6. Surgery:

- When all else failed, large bifrontal craniectomies have been performed to decompress the intracranial contents under conditions of massively increased and medically unresponsive intracranial pressures.
- Acute obstructive hydrocephalus may require an insertion of lateral ventricular catheter.

_ TETANUS

- Tetanus is an acute, often fatal disease caused by exotoxins (tetanospasmin) produced in Clostridia tetani infection.

A. Pathogenesis

- ***Cl. tetani*** is an anaerobic, spore-bearing, gram-positive bacillus.The spores are found in faeces, soil, dust, and on instruments.The usual mode of entry is through a puncture wound or laceration. The spores may then germinate and produce the exotoxin. This then travels up peripheral nerves or via the blood system and lymphatics to the central nervous system and interferes with inhibitory synapes.

B. Clinical Features

- Incubation period varies from 2-60 days (usually <15 days).
- Prodrome of fever, malaise and headache may be present. Initial symptoms are pain and stiffness in the jaw, abdomen or back, and difficulty in swallowing often perceived as a sorethroat. Later classical symptoms may develop: Trismus (the patient cannot close his mouth); risus sardonicus (a grin-like posture of hypertonic facial muscles); opisthotonus (arched body, with hyperextended neck); Spasms, which at first may be induced by movement, injections, noise etc (reflex spasms), but later are spontaneous; they may cause dysphagia and respiratory arrest; autonomic dysfunction (arrhythmias and wide fluctuations in BP).
- Patients are typically alert and conscious without sensory involvement.
- The shorter incubation is associated with more severe disease and worse prognosis for recovery.
- Localized tetanus can occur, with spasticity of a group of muscles near the wound but without trismus. The spasticity may persist for weeks. They usually resolve without sequelae. Some may progress to generalized tetanus.

C. Investigation

- There are no laboratory tests specific to tetanus. Cl tetani is cultured from the wound only in a third of cases.

D. Management

I. Treatment of tetanus

1. **General measures**:

- ***Wound care*** - The wound is cleaned and dressed. Necrotic and contaminated tissue is debrided.
- ***Supportive measures*** include ECG monitoring, shielding from unnecessary irritant stimuli, airway protection, skin and bladder care as well as maintenance of hydration and nutrition status.

2. **Antibiotic** - Recommended antibiotic regimens include:

- ***Metronidazole*** IV 500mg 8 hrly.
- ***Penicillin G*** 2-4 mega U IV 6hourly.
- ***Erythromycin*** 500mg qid orally.
- ***Tetracycline*** 500mg qid orally.

Antibiotics should be given for a total duration of about 10 days.
The antibiotic of choice is metronidazole. Penicillin may worsen gama-aminobutyric-induced hypertonia.

3. **Antitoxin**:

- ***Human tetanus immune globulin*** should be given at a dose of 3000-10,000U intramuscularly at multiple sites to neutralize free toxin. It does not affect toxins already fixed in the CNS, ie it does not ameliorate symptoms already present.

4. **Control of spasms**:

- ***Diazepam*** is the drug of choice. It can be given as IV infusion of 0.05-0.2mg/kg/h (mix 40mg in 500ml of D5%) or as IV slow bolus of 10-20mg q3h. Less severe cases can be controlled with 5-10mg q2-4h orally.
- Alternatively, continuous infusions of ***lorazepam*** at a dose of 0.1-2mg per hour or ***midazolam*** at a dose of 0.01-1mg/kg/hour can be given.
- ***Endotracheal intubation and controlled ventilation*** is indicated in severe spasms or respiratory failure. Patients are paralysed for at least 10-14 days. Most patients start to recover by the third week of illness. Tracheostomy may be needed if patients require more than 10 days of intubation.
  N.B. Where spasm seems frequent, exclude nociceptive stimuli precipitating this, such as pharyngeal secretion, pain, urinary retention, etc. Removal of these irritant would eliminate the spasm and prevent over sedation.

5. **Autonomic Dysfunction**:

- Sympathetic overactivity (eg. hypertension) can be controlled by alpha or beta blockers eg. propanolol, labetolol ,etc. Atropine is given for parasympathetic predominance.
- Hypotension may require IV fluids or pressor agents.
  N.B. Under or inadequate sedation could simulate autonomic dysfunction secondary to tetanus.

II. Immunoprophylaxis

1. **Active Immunization** with Tetanus Toxoid (TT)

- Primary immunization in children is accomplished with Triple Antigen at 3, 4 and 5 months of age.
- Primary immunization of adults: 0.5ml TT IM repeated at 6 weeks and again 6 months after the second dose.
- Booster immunization should be given routinely every 10 years.
- Following injury, an extra dose of 0.5ml TT IM should be given :
  i) For clean, minor wounds - if >10 years have elapsed since the last booster dose or the last dose of the basic immunization.
  ii) For all other wounds -if >5 years have elapsed since the last booster dose or the last dose of the basic immunization.

If tetanus prophylaxis is indicated during the period between the second primary dose and the reinforcing dose, a dose of toxoid should be given.
The non-immune should receive a full course of immunization.
If the immune status is unknown, assume that the patient is non-immune.

2. **Passive immunization** with Human tetanus immunoglubulin plus anti-tetanus toxoid should be given when the wound is other than clean, minor wounds:

- The immunization history is unknown or of questionable validity.
- Individuals who have received no prior tetanus toxoid, or who have received only one tetanus toxoid.
- The interval since the third dose of immunization or the last booster dose is >10 years; and a delay of >24 hours has occurred between the time of injury and initiation of specific tetanus prophylaxis; and the injury is of type that could readily lead to fulminant tetanus.
- Give 250-500 Units IM.

_ ALCOHOL WITHDRAWAL

- Alcohol withdrawal syndrome emerges after a period of relative or absolute abstinence from alcohol in the presence of ethanol-induced cellular tolerance.

A Clinical Features

1. Minor Withdrawal:

- Symptoms usually appear a few hours (5-10h) after reduction or cessation of alcohol consumption and resolve within 48-72 hours.
- Symptoms are characterized by autonomic nervous system dysfunction (eg. tachycardia, tachypnoea, fever, hypertension, diaphoresis, tremulousness), GI symptoms (eg. anorexia, nausea, vomiting), behavioural changes (eg. restlessness, irritability, agitation), cognitive function impairment (eg. distractability, poor memory), weakness, insomnia, nightmares, feeling of anxiety, etc.
- Anxiety, insomnia, and mild levels of autonomic dysfunction may persist for 6 months or more.

2. Delirium tremens:

- Symptoms usually appear 72-96 hrs after cessation of drinking and generally starts to resolve within 3-5 days.
- Seen in 5-10% of alcohol withdrawal and mortality is 5%.
- Manifested by tremulousness, hallucinations, agitation, confusion, disorientation, and autonomic overactivity, including fever, tachycardia, and profuse perspiration.

3. Withdrawal seizures ('Rum fits'):
- Occur 12-48 hours after cessation of intake and are usually generalized motor seizures.

B. Management

1. General measures: Abstinence from alcohol, rest, adequate nutrition, reality orientation, care of airway, etc.

2. Hydration:
- Free oral fluids if tolerating. If patient is not able to take orally, maintenance IV fluids may be adequate. Watch out of overhydration.
- Correct any electrolyte imbalance.
- Severe liver disease may result in hypoglycaemia, and starvation may result in ketoacidosis. Glucose should be administered early, either as a bolus or 25-50g (if the patient is comatose) as a dextrose plus electrolyte solution.

3. Vitamin supplementation:
- ***Thiamine*** 50-100mg IM should be given prior to glucose for 3 days followed by oral thiamine 100mg daily.
- Folate, multivitamin, vitamin B complex should also be given.

4. Sedation:
- Benzodiazepines are the drugs of choice because they do not lower the seizure threshold. They should be used on an as-needed basis.
- ***Diazepam:*** 5-20mg orally every 2-6 hrs depends on severity with maximum of 80-100mg daily. IV diazepam slow bolus can be given in severely agitated patient. Once withdrawal symptoms have abated, taper the dose gradually over a period of 1-2 weeks.
- ***Chlordiazepoxide***, 25-100mg IV or orally, repeated every 2-6 hours as needed with maximum of 500mg in the first 24 hours. Halves the dose over the next 24 hours and then reduces the dose by 25-50mg / day each day thereafter.
- ***Chlormethiazole***, 4-10g / day in 3-4 divided doses. IV preparation can also be given if needed. Decrease the dose by 20% on successive days over a period of 3-5 days.
- ***Beta-adrenergic blockers*** eg. atenolol 100mg daily can be used as adjunct to benzodiazepines to treat autonomic hyperactivity.
- ***Antipsychotic*** medications such as thioridazine or haloperidol are sometimes used for delirium tremens.

5. **Seizures control**:

- Withdrawal seizures respond to oral or IV benzodiazepines, if they are frequent, phenytoin or barbiturates can be effective in the acute setting. Treatment with chronic anticonvulsant drugs is not indicated. Other causes of seizures need to be excluded.

6. **Search for and treat complicating illnesses.**

_ NEUROLEPTIC MALIGNANT SYNDROME

- NMS is a catatonic like state associated with fever (hyperthermia), altered mental status, muscle rigidity, and autonomic dysfunction seen in patients taking neuroleptic agents. It may also occur in patients who withdraw from antiparkinson medications and patients who use recreational drugs.
- NMS may occur within hours of taking neuroleptic but usually occurs within the first 2 weeks of treatment with neuroleptic agents. NMS is more likely to occur if rapid increase in dosage is done, IM depot preparation is used and concomitant use of other drugs like lithium. NMS can also occur at any time during antipsychotic drug use.
- Most commonly implicated neuroleptic agents are low dose high potency neuroleptic agents (eg. haloperidol, fluphenazine).

A. Clinical Features

1. Core symptoms:
- Fever, often >40^{o}C.
- Severe muscle rigidity - typically 'lead pipe' or 'plastic' type of rigidity.
- Altered consciousness - clouding of sensorium, possibly progressing to stupor or coma.
- Autonomic instability - labile pulse and blood pressure, diaphoresis, tachypnoea, pallor etc.

2. Additional symptoms: tremor, dyskinesia, akinesia, oculogyric crisis, opisthotonos, and chorea. Hypertonic pharyngeal musculature may lead to dysarthria, dysphagia, sialorrhoea, and respiratory complications. Babinski's signs and generalised tonic-clonic seizures are occasionally seen.

3. Laboratory Features:
- Elevated CPK to 2000-15,000U .
- Leukocytosis - 15,000-30,000 / ul with a shift to the left.
- EEG usually normal.
- Liver function- occasionally, liver enzyme elevation is found.

4. Complications:
- Renal- Rhabdomyolysis with myoglobinuria and acute renal failure.
- Cardiac- Cardiac arrest or MI with pulmonary oedema.
- Pulmonary- hypoxia, aspiration and pulmonary embolism.
- Others- anterior tibial syndrome, infections, hepatic failure and DIVC.

B. Investigations

- FBC, TWDC, BUSE, Se Calcium, CPK, ABG, urinalysis, urine myoglobin, coagulation studies, ECG, CXR, lumbar puncture if meningitis is suspected.

C. Differential Diagnosis

- ***Endocine:*** Hyperthyroidism
- ***Environmental:*** Heat stroke
- ***Infections:*** Meningitis
  Encephalitis
  Sepsis
  Tetanus
  Rabies
- ***Neuromuscular*** Malignant hyperthermia
  Parkinson disease
  Severe dystonia

- ***Toxic:*** Amphetamines
  Cocaine
  Anticholinergics
- ***Serotonine syndrome:***
  MAO inhibitors.
  Selective Serotonin receptor inhibitors (SSRI)

D. Treatment

1. Supportive measures:

- ICU monitoring.
- The offending drug should be withdrawn.
- Antipyretics, cooling blankets, ice packs to return the temperature as close to normal as possible.
- Supplemental oxygen with or without mechanical ventilation as needed to support the patient's respiratory status.
- IV fluids should be given initially for hypotension. A urine output of 30ml/h or greater should be maintained.

2. Pharmacotherapy:

- ***Bromocriptine:*** 2.5-10mg 3X daily up to 60mg/day.

Bromocriptine may be used in conjunction with dantrolene with similar dosage patterns.

- ***Dantrolene:***
  IV with initial dose of 1-3mg/kg over 10-15 mins as needed to alleviate rigidity and should not exceed 10mg/kg/day.

  or

  Orally or NG with initial dosage range from 100-200mg/day (in divided doses eg. 50-100mg bd) up to 700mg/day may be given.
- ***Alternative therapy:***
  Amantadine 200-400mg/day in two divided doses.
  Benzodiazepines**:** eg. lorazepam 2mg IV and 2mg in repeated doses (or diazepam) if necessary.

- In cases associated with withdrawal of dopamine agonists (eg. L-dopa, bromocriptine) reinstitution of dopaminergic therapy and more gradual withdrawal should be undertaken.
- In cases following psychotropic therapy, Electro Convulsive therapy might be indicated in stubborn cases.

3. Re-treatment strategies:

- If neuroleptics are needed, institute treatment as long as possible after an episode of NMS. Try a neuroleptic from a different family (if possible, a low-potency agent). Start with a low dose in hospital setting and gradually increase the dose. The patients should be monitored clinically and also with CPK levels.

– GUILLAIN BARRE SYNDROME (ACUTE IDIOPATHIC DEMYELINATING POLYRADICULONEURITIS [AIDP])

A. Antecedent events / associated diseases

- Acute infectious disease: Campylobacter jejuni, viral (viral exanthems, CMV, EBV, HIV), myocoplasma
- Surgery.
- Immunization.
- Hodgkin's lymphomas.
- Systemic lupus erythematosus.
- Thrombolytic agents (rare).

B. Clinical features

- Usually preceded by acute illness, as mentioned above.
- Mainly motor polyneuropathy, often progressive and ascending over 3 days to 4 weeks but it may come on rapidly and affect all 4 limbs simultaneously. Proximal muscle may be more affected.
- Trunk, respiration and cranial nerves (especially VII) may be affected.
- Sensory symptoms are common but signs usually difficult to detect.

- Areflexia occurs early and is generalized.
- Bladder or bowel dysfunction at the onset or persisting during the disease is rare.
- Autonomic dysfunction can cause cardiac arrhythmias.

C. Investigations

- The increase in CSF protein with less than 10 cells / ml strongly supports the diagnosis when found after the first week of symptoms or when a progressive rise of protein content is demonstrated from several lumbar punctures.
- Nerve conduction studies usually show a demyelinating pattern but may occasionally show primary axonal pattern.

D. Management

1. General management:

- ***Monitor vital capacity*** (not peak expiratory flow): intubation and ventilation if breathless or vital capacity <20ml / kg or VC drops to 25-30% of normal (Normal vital capacity in males = 25cc X height in cm; females = 20cc X height in cm).
  N.B. There should be a low threshold for ventilation. Remember, pharyngeal paralysis without respiratory muscle weakness must be excluded. The treatment here is a tracheostomy with a protected cuffed portex tube.
- ***Monitor ECG & BP*** - Tachycardia with loss of sinus arrhythmia are usual, rapid fluctuations of pulse and BP may occur. Tracheal suction may cause bradycardia and asystole - this can be prevented by hyperoxygenation beforehand but if it persists it may be necessary to use atropine.
- ***ABG*** should be done periodically.
- ***Subcutaneous heparin*** 5000U bd daily in paralyzed patients.
- ***Chest physiotherapy.***
- ***Prevent contractures:*** passive movements, ankle splints, hand-wrist finger splint.
- ***Hydration/nutrition*** via nasogastric tube.
- ***Urinary catheter.***
- ***Analgesia:*** including amitriptyline, carbamazepine, NSAIDs, opiates.

2. IV immunoglobulin:

- It is now consider the first choice of therapy for most patients. It should be offered to all patients who have severe disease that they are unable to walk or requiring respiratory support.
- The rate of recovery is similar in patients treated with IV Ig compared to those treated with PE.
- Although IV Ig is expensive, it is not usually more expensive than PE and it is more widely available and simpler to give.

- IV Ig is given either as 0.4g/kg daily for 5 days or 1g/kg daily for 2 days.
- IV Ig should be used with extreme caution or avoided in patients with pre-existing renal failure which it may exacerbate. Other adverse effects are headache, chills, myalgia, chest discomfort, fatigue, exhaustion, fever, skin reactions, aseptic meningitis, severe anaphylactic reaction in those patients with absent or severely decificient IgA and thromboembolic events.

3. Plasma exchange/Plasmapheresis:

- Plasma exchange can be of ferred to patients with GBS who have severe disease that they are unable to walk or requiring respiratory support but have relative contraindications to the use of IV Ig.
- It should be given as early as possible although so long as the disease is still progressing it would be worth using PE.
- The usual course is 5 exchanges every other day over a period of 8-10 days.

4. Corticosteroids:

- Oral prednisolone or IV methylprednisolone has not been demonstrated to be beneficial in GBS.

6. ENDOCRINOLOGY AND METABOLIC DISEASE

_ HYPOGLYCAEMIA

Symptoms usually occur when blood glucose <2.8mmol/L (50 mg/dL) for patients with normal initial blood glucose. The nature of symptoms depend on the absolute level of glucose and the rate of fall to this level.

A. Predisposing factors

1. Insulin or oral hypoglycaemic agent (OHA) "overdose".
2. Changes in content or timing of meals.
3. Increased physical activity.
4. Renal failure with decreased clearance of insulin and OHA.
5. Onset of certain disorders eg. Addison's disease, hypopituitarism, liver cirrhosis / failure and malabsorption.

B. Symptoms and Signs

- **Early:**
  Shaking, trembling, sweating, palpitations, hunger, pins and needles in lips and tongue.
- **Neuroglycopenia:**
  Difficulty in concentrating, change of behaviour, confusion, seizure, stupor, coma or focal neurological signs simulating cerebrovascular accidents or transient ischaemic attacks.

C. Management

1. Treatment of hypoglycaemic episodes: Prevention is better than cure, and correction should be as quick as possible.

a. Fully conscious patients:

- Oral glucose, sucrose, or sugar-containing fluids eg. 1-2 tablets of glucose / sweets, 1-2 cups of milk, orange juice, piece of fruit, cheese etc. Ensure adequate subsequent food intake to prevent relapses.

b. When mental function is impaired:

- IV 50% dextrose 25-50ml, or as much as possible until mental functional recovery or blood glucose estimation shows a normal level, followed by infusion of 5-10% D / W or a glucose drink, if the patient recovers full consciousness.
- When hypoglycaemia is due to an overdose of long-acting insulins or OHA, 10% dextrose drip should be continued for 24-48 hrs to maintain satisfactory blood glucose level.

- Blood glucose should be maintained between 90-120 mg / dL (5-6.7mmol / L).
- Glucagon, 1mg IM or SC can be given to treat severe hypoglycaemia when IV access is difficult. This treatment option can also be taught to relatives of patients on insulin, with episodes of severe hypoglycaemia. As soon as the patient regains consciousness after glucagon, they are advised to eat / drink something as the hyperglycaemic action of glucagon lasts only 10-15 minutes.
- Patients who remain unconscious after prolonged hypoglycaemia may need to be given treatment for cerebral oedema with IV dexamethasone 4mg 6hrly or IV mannitol.

2. Adjustments of drug therapy, diet and physical activity:

- If hypoglycaemia recurs at a particular time of day- change the distribution and timing of insulin injections.
- If hypoglycaemia is severe, prolonged, or unpredictable, reduce total dose.
- Increased carbohydrate intake prior to increased or prolonged activity / exercise.

3. **When the crisis is over**, deal with the cause to prevent a recurrence.

_ DIABETIC KETOACIDOSIS

- *Diabetic Ketoacidosis is a state of absolute insulin bankruptcy*.

A. Clinical features

- Progress over a short period of time (usually few days)
- Polyuria & polydipsia
- Vomiting
- Abdominal pain
- Weight loss
- Drowsiness
- Dehydration
- Hyperventilation
- Acetone on breath
- Hypotension
- Coma

- ***Usually due to:***
  1. Stopping insulin or reducing the dose.

2. Onset of unrecognised insulin-dependent diabetes.
3. Stress, with increasing insulin resistance and requirement eg. infections, trauma, surgery, myocardial infarction, stroke, etc.

B. Investigations

- ***Tests are carried out to:***
  - ***a. Measure the biochemical parameters to diagnose the syndrome.***
  - ***b. To delineate the aetiological basis for the ketoacidosis.***
  - ***c. To monitor the impact of therapy.***
- ***FBC*** - white count is often raised to 15-20x10^9/L, and is NOT necessarily indicative of a bacterial infection
- ***Blood glucose*** - might vary from 10 mmol/litre to extreme hyperglycaemia (N.B. blood glucose level may not correlate with severity).
- ***Serum Na & K*** - K is usually raised. Na may be normal or reduced.
- ***Urea & creatinine*** - often raised due to dehydration, with urea increased disproportionately to se creatinine.
- ***Urine*** - glycosuria & ketonuria.
- ***Acid-base status*** - pH ranges from normal to 6.9 with low bicarbonate.
- ***Plasma ketones*** - usually strongly positive with ketostix.
- ***Investigations to delineate the cause*** eg. CXR, infective screen, ECG, urine microscopy.

C. Management

 # The goal of management is to correct:
- Fluid loss (average: 90-120ml/kg).
- Electrolyte losses - K (around 3mmol/kg) & Na (around 7-10 mmol/kg).
- Hyperglycaemia.
- Acidosis.

1. Correct hypovolaemia/dehydration.
- Average of 6-8 litres may need to be given for the first 24 hrs.
- Suggested regime for ***moderately dehydrated*** patients:

  Normal saline 0.9%(154mmol/L Nacl)

  1 litre in 1 hour
  then 1 litre in 2 hours
  then 1 litre in 4 hours
  then 1 litre in 6 hours
  then 1 litre in 8 hours

  N.B. The regimen is a guideline. The replacement must be done with close monitoring of the patient's clinical state, and response, including laboratory results. The regimen often have to be customised to individual patients.

- If patient is in shock, fluid administration should be normal saline or colloids administered at a rate that is necessary to restore circulatory function.

- Monitor patient closely and look out for fluid overload or underhydration, CVP line is helpful particularly in the older patients or where massive fluid replacement might be indicated.
- When serum Na level >150mmol/L, use 0.45% Nacl.
- When blood glucose is <15mmol/L, change to fluid containing glucose such as dextrose saline or 5-10%dextrose water or alternating dextrose saline and 5% dextrose depending on Na level (Use 10% dextrose if significant metabolic correction is still needed eg persisting acidosis).
- Further lowering of the plasma glucose from 12-15 mmol/L to 5-10 mmol/L should be done over the next 12-24 hours as too rapid lowering of plasma glucose to normal may precipitate cerebral oedema.

2. Insulin therapy:

- Continuous intravenous insulin infusion is the treatment of choice. Soluble insulin is diluted in 0.9% saline (not dextrose) at a concentration of 1U/ml. Give IV bolus 10U soluble insulin whilst the infusion is being prepared. Give 6U/hr (0.1U/kg/hr) by infusion pump or paediatric drip set after IV loading. Adjust the infusion rate as below. Blood glucose should be monitored hourly and should be continued till the patient's metabolic state is virtually normal and oral feeding is restored.

Blood glucose (mmol/l)	Insulin infusion rate (ml/hour)	IV fluid
<5	0-0.5	Dextrose
5-10	1-2	Dextrose
10-15	2-3	Dextrose
15-20	4	Normal saline
>20	6 & review	Normal saline

- Intramuscular insulin injections can be used as an alternative or when an infusion pump is not available. Soluble insulin 20U IM stat then 6U hourly IM and adjust the doses as in IV insulin infusion or to give insulin 2 hrly when glucose <15 mmol/L. This regime is not suitable in patients who are hypotensive and peripheral circulation is compromised.

With the above regime, glucose levels should fall by at least 3mmol/L/hr (50mg/dl/hr), a slower response indicate insulin resistance or inadequate fluid administration.

If insulin resistance is suspected, dosage of IV insulin should be increased by 50-100% in hourly increment.

When dextrose is given, the plasma bicarbonate and anion gap are more appropriate measures of insulin effect. Insulin can be tapered, with care to maintain the basal requirements (eg.1-2U/hr) when plasma bicarbonate rises to >15mmol/L and the anion gap resolves.

3. Potassium replacement:

- Although hyperkalaemia may be observed initially due to metabolic acidosis, patients with DKA usually have low total body potassium, and life-threatening hypokalemia can develop following insulin treatment.
- Give no potassium replacement in the first litre of fluids whilst awaiting plasma potassium level.
- Administration of potassium should begin:
  - ***a. When ECG shows no evidence of hyperkalemia,***
  - ***b. When ample urine output is demonstrated &***
  - ***c. When plasma K is <5mmol/L.***
- Add 1gm KCL in each 0.5 litre of fluid initially.

Adjust potassium replacement according to serum potassium level as in table below.
Do BUSE 4-6hrly and ECG monitoring.
Serum potassium should be maintained between 4-5mmol/L.

Plasma potassium (mmol/l)	Potassium added (mmol/l)
<3	40
3-4	30
4-5	20
>5	Give none

4. **Bicarbonate therapy,** should be considered when:
   a. ***Arterial pH < 6.9.***
   b. ***DKA is accompanied by shock (SBP<90mmHg) or coma when pH < 6.9-7.0, unresponsive to volume repletion.***
   c. ***Severe hyperkalaemia is present.***

- A solution of sodium bicarbonate mixed with normal saline or 0.45% saline is preferred than bolus infusion.
- Amount of NaHCO3 needed (mmol/L) = 1 to 2 ml of 8.4% NaHCO3 per kg of body wt over 30 min and recheck ABG.
  1ml of 8.4% NaHCO3 = 1mmol/L of NaHCO3.
  Additional potassium supplement is required whenever alkali are given.

5. **Phosphate** - Hypophosphataemia occasionally occurs in DKA. It causes general debility and anergy and should be corrected.

6. **Recognition and treatment of precipitating factors.**

- Search for and treat precipitating conditions. If sepsis is suspected, treat with a broad spectrum antibiotic until culture results return. Then witch to appropriate antibiotic.

7. **Be alert for complications of DKA:**
   Hypoglycaemia.
   Cerebral oedema.
   Arterial or venous thrombosis (Give SC heparin 5000U 12hrly until patient is well enough to walk).
   Hypokalaemia.
   Gastric dilatation, secondary to gastroparesis. In most instances, in the unconscious patients, continuous NG aspiration to keep the stomach empty might be necessary.

8. **Recovery:**

a. ***Long term insulin therapy*** is required in virtually all patients who experience diabetic ketoacidosis except those with DKA secondary to severe stress ie gangrene/septicaemia.

b. ***Changeover from infusion to SC insulin:***

- Continue insulin by infusion until urinary ketones are negative or only 1+ (usually correction of acidosis lags behind glycaemic control and takes about 24-48 hours).
- The patient may then take food with soluble insulin given SC. Continue the infusion for 1 hour after the first SC dose.
- Start with short-acting (soluble) insulin three times daily before meals and intermediate-acting insulin at bedtime. Base the total daily dose on double the total dose insulin given over the last 12 hours.
- Check blood glucose pre-meals & pre-bed and adjust insulin dose accordingly.
- When insulin requirements are stable, continue basal bolus regime or change newly diagnosed diabetic patients to a twice daily insulin regimen. Put known diabetic patients back on their usual regimen.

HYPERGLYCAEMIC HYPEROSMOLAR NON-KETOTIC COMA

- *Unlike ketoacidotic coma, there is relative insulin insufficiency resulting in marked hyperglycaemia but no or minimal ketone formation.*

A. Clinical features & investigations

- ***Occurs only in Type II DM***
- Could be initial presentation of the diabetic state
- Patients are often elderly
- Severe dehydration invariable
- Coma to obtundation
- Blood glucose usually >50mmol/L
- Absence or trace of ketonemia
- Osmolarity of >320 mOsm/liter (The result of water loss being disparately greater than electrolyte losses)
- Azotaemia
- May have associated lactic acidosis
- Precipitating factors similar to DKA
- Mortality rate is high

B. Management

1. Take blood for investigations as in DKA.

2. Correct dehydration, **hyperosmolality** and **Na and K depletion:**

- A CVP is usually necessary to aid assessment of fluid replacement.
- Fluid and electrolyte loss can be as great as 25% and we should aim to replace half this loss in the first 12h and the rest in the ensuing 24h.
- The choice of replacement fluid is 0.9% normal saline. Use 0.45% Nacl if serum Na >150mmol/L (hypernatraemia).
- After volume is restored and hyperglycaemia has responded to insulin therapy, a 5% dextrose solution can be given to patients with persistent hyperosmolarity and hypernatremia (see section on hypernatraemia).

- K deficit should be anticipated during insulin treatment and should be replaced as in DKA.

3. Insulin therapy:

- The patients are extremely sensitive to insulin hence only low doses need to be used.
- Blood glucose should be lowered more gradually than in DKA (as risk of cerebral oedema is more likely).
- Give 10U IV bolus soluble insulin followed by continuous infusion at a rate of 3U/hr and reduced accordingly as shown in table below (increased to 6U/hr if there is poor response in glucose reduction).

Blood glucose (mmol/l)	Insulin infusion rate (ml/hour)	IV Fluid
<5	0-0.5	Dextrose
5-15	1	Dextrose
15-20	2	NS or 1/2 NS*
>20	3	NS or 1/2 NS*

* *Depends on serum Na level.*

4. Prevention of venous and arterial thromboses:

- Heparinize patient for 2-3 days eg. SC 5000U 8hrly.

5. Look for and treat precipitating events.

6. After the acute episode, the patient can usually be controlled with diet either alone or with small doses of oral hypoglycaemic agents.

THERAPY OF DIABETIS MELITUS IN SURGICAL PATIENTS

- Good blood glucose control is necessary to ***(i) avoid symptomatic hyperglycaemia or hypoglycaemia and their acute complications (ii) allow a normal inflammatory response and wound healing.***
- Minor surgery is defined as a procedure after which the patient may be allowed to eat and drink within 4 hours; all other procedures are classified as major.
- The surgical senario could be (A) elective or (B) emergency.

A. Elective surgery

1. Major surgery:

- Admit to hospital 2 to 3 days before operation.
- Establish good preoperative control (a twice daily mixture of short and intermediate acting insulin is acceptable or maintain the basal-bolus regime).
- Monitor blood glucose pre-meals and pre-bed.
- Schedule the timing of the operation for the early part of the day to avoid prolonged fasting.

- ***Two methods are available:***

a. Dextrose drip and variable-rate insulin infusion

- Give the usual prescribed insulin on the night before the operation.
- Perform a blood glucose stat in the morning.
- Omit the morning dose on the morning of operation. Start infusion of dextrose 5%, add 1g KCl to each litre, and run at a constant rate appropriate to the patient's fluid requirements, usually 125ml/hr.
- Make up a solution of soluble insulin 1U/ml saline in a syringe and infuse IV using infusion pump or paediatric drip set (50U in 50ml of 0.9%). The suggested infusion rate is as shown below:

Blood glucose (mmol/L)	**Infusion rate**
<5	0-0.5U/h
5-10	1-2U/h
10-15	2-3U/h
15-20	4U/h
>20	6 & review

 # Adjust the insulin infusion rate according to the response as shown by serial monitoring.

 # Do not change insulin infusion rate if blood glucose level ranges between 5-10 mmol/L.

 # This is only a guide and different patients may respond differently.

- In some circumstances, higher doses of insulin infusion will be needed (up to 2x or 3x of above infusion rate) eg. in patients with severe infection, in cardiac surgery, if adrenergic agent is being used, in patients on high doses of corticosteroids.
- Measure blood glucose levels 2hourly until stable (5-10mmol/L is ideal) then 4 hourly. However, do at least once during surgery; each hour, if surgery takes >1 hour; at least once in the recovery area.
- K level should also be monitored and adjusted accordingly.
- Continue the regimen until the patient is eating and then switch back to the previous regimen. The usual SC insulin regimen may need to be modified until a full diet is resumed; control may initially be easier using a regimen of short-acting insulin given before meals & intermediate acting insulin at bedtime (basal bolus) as this allows greater flexibility and adjustments can be made more quickly.

b. Glucose-insulin infusion (when no pump is available):

- Give the prescribed dose of SC insulin on the night before the operation.
- Omit the morning dose on the morning of operation. Begin an infusion of dextrose 5% containing 1g KCl and soluble insulin 16 units per litre initially. Run it at a rate appropriate to the patient's fluid requirements, usually 125ml/h. Adjust insulin dose added to dextrose 5%as follows:

Blood glucose (mmol/L)	Infusion rate
<5	0-4U insulin/L
5-10	8 U insulin/L
10-15	16U insulin/L
15-20	32U insulin/L
>20	64U & review

- Glucose monitoring as in **1** (mentioned earlier).

2. Minor surgery:

- List the patient early, to prevent unnecessary prolonged fasting.
- Follow the above preoperative regimen. Omit insulin on the day of operation. Do preoperative, immediate postoperative and 4 hrly postoperative blood glucose estimations.
- Give soluble insulin on return from theatre when the patient can take oral carbohydrate, 50% of usual dose, should be given by noon.
- Give normal evening insulin.
- Use soluble insulin intravenous regime if blood sugar >15mmol/L.

II. Non-insulin-dependent diabetics

a. ***If the patient's glucose is well controlled*** (random blood glucose < 12-15, fasting < 9-10 mmol/L)

- Fast the patient as usual.
- Omit the tablet on the day of operation.
- Check the blood glucose concentration before and soon after operation; if the blood glucose value is over 12 to 15mmol/L start soluble insulin subcutaneously, eg. 6-10 U of soluble insulin.
- Oral hypoglycaemic agents should be reintroduced when oral intake is resumed.
- If a major operation is planned or if postoperative 'nil by mouth' is likely to prolonged, it is best to use insulin and glucose infusions as for insulin-dependent diabetics.

b. ***If the diabetes is poorly controlled*** (random blood glucose >15mmol/L), the patient should be started on insulin before the operation, using one of the regimens described above.

B. EMERGENCY SURGERY

- In the event that emergency surgery is indicated, there might be no time to establish good metabolic control. In such a situation, the priority is to correct the volume/electrolyte state as best as possible, particularly the potassium level; acid base would have to be corrected till it is not dangerously deranged. The surgical procedure might then be allowed to commence. The glucose level can be tackled during and after the surgical

procedures. To address these problems, the operation may need to be delayed for 4-6 hours.

_ MYXOEDEMATOUS COMA

A. Symptoms and Signs

- Most patients are female
- Commoner in cold countries
- Usually elderly
- Looks hypothyroid
- Hypothermia
- Hypotension
- Hyporeflexia
- Bradycardia
- Comatose
- Fits
- Hypoventilation
- Hypothermia
- A stroke or use of some sedative depressant medications might be identifiable.

B. Investigations

- Hypoglycaemia
- Hyponatraemia / occasionally a SIADH-like picture
- Macrocytic anaemia
- Hypoxaemia
- Hypoadrenalism

C. Management

1. **Take** free T3, free T4, TSH, FBC, BUSE, blood C&S, urine microscopy & culture, ABG, blood glucose.

2. Treatment should be started on **clinical grounds,** if in genuine doubt, it is worth treating as for myxoedema coma, as giving L-thyroxine judiciously is unlikely to be harmful in the short term.

3. **Thyroid hormone replacement:**

- Replacement of thyroid hormone should be gentle as patients are elderly and liable to cardiac arrhythmias, heart failure or infarct.
- Whether T4 or T3 or both should be given is controversial,T3 has faster duration of action, whereas T4 replacement is easier and more reliable and its action is smoother.
- ***T4*** - IV 200mcg bolus followed by daily dose of 100mcg until patient can take orally (oral T4 may be given if T3 or IV T4 and is not available but the action is too slow).

- ***T3*** - IV or oral by NG tube 10-20 micrograms 12hrly until T4 can be given orally.
  # If ischaemic heart disease is suspected , the dosage of both the above should be halved.

4. **Steroids** - All patients should be given 100mg hydrocortisone IV stat and then 50-100mg 8hrly as these patients may have impaired reponse to stress due to impaired ACTH secretion.

5. **Ventilation -** If PaO_2 is<60mmHg (8.0kPa) with O_2 or if $PaCO_2$ is >40mmHg(5.3kPa), assisted ventilation may be required.

6. **Hypothermia** - Do not warm the patient rapidly. This may cause cardiovascular collapse. Use lots of blankets and monitor the rectal temperature. Do not correct faster than 1^{o} C per hour. A low reading thermometer would be needed.

7. **Hypoglycaemia -** should be corrected.

8. **Hypotension -** If present , plasma expanders should be given. CVP line may be needed.

9. **Hyponatraemia** - nearly always caused by dilution and redistribution. Appropriate treatment is fluid restriction. However, if Na is <110mmol/L , hypertonic saline may be given, with a maximal correction of the serum sodium by not more than 10 mmol/24 hour period.

10. **Remove or treat the precipitating causes.**

11. On **full recovery**, the dose of replacement thyroxine should be titrated once every 2 to 3 weeks to maintain a euthyroid state.

_ THYROID STORM

A. Symptoms and Signs

- Severe hyperthyroidism, high fever, agitation, sweating, confusion, coma, tachycardia, diarrhoea and vomiting, atrial fibrillation, heart failure, myopathy, acute psychosis, acute abdominal pain simulating an acute abdomen, etc

B. Precipitants

- Infection, surgery, poorly prepared thyroid surgery, diabetic ketosis, radioiodine therapy in a poorly prepared patient, trauma, myocardial infarction, amiodarone etc.

C. Management

 # The mortality of untreated thyroid storm is high, if the diagnosis is suspected, antithyroid treatment must be started before biochemical confirmation.

1. Take blood for FBC, BUSE, blood glucose, free T3, free T4 and investigate for precipitants.

2. Hyperthyroidism:

a. Inhibition of thyroid hormone formation.

- ***Propylthiouracil*** 900-1200mg / day orally or NG tube in 3-4 divided doses (eg. 150-300mg 6hrly reduced to 100-200 mg 8hrly after 24-48 hrs).

  or

  Carbimazole 60-120mg / day in 3-4 divided doses orally or NG tube (eg. 15-30mg 6hrly reduced to 10-20mg 8hrly after 24-48hrs).

b. Inhibition of thyroid hormone release:

- ***Sodium iodide*** IV 1gm / 24 hrs by slow infusion

  or

  Oral potassium iodide 100mg 6hrly

  or

  Oral Lugol's iodine 10-20 drops 8hrly

  (Iodine should be given 1hour after the patient has received the initial dose of propylthiouracil or carbimazole and is to ensure that the iodine given is not taken up by the gland for further thyroid hormone synthesis and release)

3. Steroids - IV ***dexamathasone*** 2mg 6hrly. Dexamethasone inhibits both release of thyroid hormones and peripheral conversion of T4 to T3.

4 Receptor blockade(in the absence of heart failure):

- IV ***propanolol*** 1-2mg slowly 4-6hrly or oral propanolol 40-80 mg 6hrly (Propanolol should not be used if there is pulmonary or peripheral oedema and should heart failure supervene, atropine 0.4-1mg IV should be given). Assessment of LV function will help guide the use of beta-blockers.
- ***Diltiazem*** 60-120mg 6hrly PO can be used if beta-blockade is contraindicated eg. in bronchial asthma.

5. Cardiac failure:

- Usually associated with fast atrial fibrillation.
- ***Diuretics, digoxin, oxygen*** as appropriate and ***propanolol*** if cardiac failure is due to uncontrolled atrial fibrillation and LV function is good.
- There is relative digoxin resistance with increased renal excretion & decreased action on A-V conduction, so a higher dose of digoxin may be needed.
- ***Cardioversion*** of AF is very unlikely to be successful and should wait until the patient is euthyroid.
- ***Amiodarone*** may be useful when given parenterally to control acute arrhythmias.

6. Hyperpyrexia:

- Fans, tepid sponge, paracetamol and etc. Aspirin should not be used.

7. Dehydration:

- Cautious replacement of fluid. CVP line is helpful.

8. Anticoagulation:

- Give heparin by infusion in patients with AF. Other patients should receive heparin 5000U 2-3 x daily SC as prophylaxis against venous thrombo-embolism.

9. Treat **severe agitation** with chlorpromazine 150mg 8hrly PO or 25mg 8hrly IM.

10. Exchange transfusion or PD/HD:

- This may be considered in a patient who fails to improve within 24-48 hrs.

_ ADDISONIAN CRISIS

A. Clinical clues

- Someone known to have Addison's disease/hypoadrenalism
- Someone on long-term steroids
- Postural hypotension or hypotension
- Generalised weakness
- Tachycardia
- Vomiting
- Abdominal pain
- Confusion
- Coma

B. Precipitating factors

- Infection, myocardial or cerebral infarction, trauma, parturition, metabolic stress, meningococcal septicaemia

C. Laboratory Findings

- Low serum Na (<130mmol/L)
- High serum K (>5mmol/L)
- Low blood glucose (<50 mg/dL or <2.8mmol/L)
- Decreased plasma bicarbonate (<28mmol/L)
- Elevated blood urea
- Low serum cortisol
- X-ray:
  Calcifications or enlargement of the adrenals
  Pulmonary or miliary TB

D. Management of addisonian crisis

1. Steroid replacement:

- If adrenal crisis is suspected, corticosteroids must be given without delay. The results of cortisol levels will not be available before starting corticosteroid therapy. The short ACTH test may be undertaken together with treatment, provided that there is no undue delay in giving the required drugs. Blood is taken for baseline cortisol levels, and other hormone and electrolyte estimates. Dexamethasone 10mg is given IV, together with tetracosactrin (Synacthen). Dexamethasone begins replacement therapy rapidly without interfering with the cortisol assay. Cortisol levels are taken at 30 and 60 mins. Corticosteroid treatment is continued as hydrocortisone.
  NB. Dexamethasone has negligible mineralocorticoid activity.
- The initial bolus dose for hydrocortisone may be 200mg IV if the short ACTH test is omitted followed by 100mg IV q6h for 1 day, 8hourly on day 2 and is tapered during recovery by decreasing one third of the daily dose

every day until a replacement dose is reached within 5 days unless the precipitating cause has not been treated fully.

2. **Volume repletion** should be started immediately (eg. 1 litre of normal saline over 2h and then dextrose saline).
- Set up CVP line if necessary. Monitor glucose closely and to give IV or oral glucose is usually necessary.
- Further fluid replacement will depend on how much salt and water depletion has occured.

3. **Fludrocortisone** 0.05-0.3mg daily should be given when the hydrocortisone dose is below 100mg / day and IV fluids are discontinued in primary addisonism.

4. **Consider the cause:**
- Do ECG, CXR, blood C&S, urine microscopy etc.
- Since bacterial infection frequently precipitates acute adrenal crisis, broad-spectrum antibiotics can be administered empirically while waiting for the results of initial cultures.

 # CAUTION

Delay in instituting corticosteroid therapy may result in mortality.
Water intoxication can easily occur in these patients if hypotonic saline is given.

E Treatment of chronic adrenal insufficiency

1. **Primary adrenal insufficiency:**

a. Glucocorticoid replacement:
- Average replacement steroid dosages for adults with primary hypoadrenalism are shown.

Drug (oral)	**Replacemant Dose**
Hydrocortisone	30 mg daily- 20mg on waking, 10mg at 1800h
Cortisone Acetate	37.5mg daily- 25mg on waking, 12.5mg at 1800h
Dexamethasone	0.75mg daily-0.5mg on waking, 0.25mg at 1800h
Prednisolone	7.5mg daily- 5mg on waking, 2.5mg at 1800h

** Dexamethasone is less frequently used due to higher incidence of Cushing's syndrome.*

- Cortisol secretion correlates with body surface area and cortisol turnover is increased in ***obesity.***
- ***Increased doses*** are also required if drugs known to enhance the metabolism of glucocorticoids are concomitantly used eg ***barbiturates, phenytoin, rifampicin.***

- ***Lower doses*** are indicated in ***significant liver disease*** (slow metabolism of glucocorticoids), ***geriatric patients, diabetes mellitus, peptic ulcer and hypertension.***
- ***Reliable indices*** in assessment of glucocorticoid replacement doses include ***appropriate weight gain and regression of pigmentation.*** Urine free cortisol or serum cortisol measurement are not reliable indicators of adequate cortisol replacemet.

b. Mineralocorticoid replacement:

- Mineralocorticoid replacement is neccesary in primary adrenal insufficiency, and dose requirements can be variable.
- ***Fludrocortisone*** is given as a single daily dose of 0.05-0.30mg (Usual dose 0.1mg/d). Dose changes are in increments of 0.05mg/day of fludrocortisone.
- ***Persistent hypotension, orthostatic hypotension, and hyperkalaemia*** are indicators that increased doses are needed, whereas ***hypertension, hypokalaemia and oedema*** indicate dose reduction.

c. Intercurrent illness or stress:

- Intercurrent illness or stress requires an adjustment of glucocorticoid therapy but not of mineralocorticoid therapy.
- For ***minor illnesses*** eg respiratory tract infection, dental extraction, glucocorticoid ***dosage is doubled*** until the condition has resolved.
- During ***major stress*** the maximum daily glucocorticoid requirement is equivalent to ***300mg hydrocortisone.***
- ***Vomiting and diarrhoea*** require hospitalization because they preclude oral intake of replacement therapy and result in rapid dehydration.
- ***Elective major surgery*** requires 100mg hydrocortisone administered IV during the night preceding the surgery, and subsequently 100mg 8 hourly until the patient has stabilized postoperatively. Medication is tapered rapidly (3-5 days) to the previous dosage.
- ***Major catastrophies*** or emergencies eg trauma, major emergency surgery, sepsis, MI require treatment ***as in acute adrenal crisis.***

2. Secondary adrenal insufficiency.

- Secondary adrenal insufficiency does not require mineralocorticoid replacement.

F. Footnotes

Short ACTH (Synacthen) test

1. Procedure:

- A blood sample is taken for plasma cortisol at 9am. 250ug of tetracosactrin (synacthen) is given IV and further blood samples are taken at 30, and 60 mins.
- Baseline ACTH level should also be taken.

2. Interpretation:

- In normal subjects:
  _ The basal cortisol should exceed 160nmol/l (6ug/dl).

_ The increment rise should be at least 190nmol/l (7ug/dl).
_ A cortisol level of 550nmol/l (20ug/dl) should be achieved during the test.
A normal response effectively rules out primary adrenal insufficiency.

- In primary adrenocortical failure cortisol levels will remain low throughout the test.
- In patients with severe secondary adrenal insufficiency, plasma cortisol increases little or not at all after the administration synacthen.
- In patients with secondary adrenal insufficiency that is mild or of recent onset, however, the test may be normal.
- When secondary insufficiency is strongly suspected on clinical grounds with a normal response to ACTH, other tests such as the metyrapone test or long ACTH stimulation can be done.

_ HYPERNATRAEMIA

A. Causes

1. **Pure water depletion (isovolaemia)**
   Inadequate water intake
   Lesions of thirst centre
   Diabetes Insipidus

2. **Hypotonic fluid loss (Hypovolaemia)**
   GI: vomiting, diarrhoea, fistula
   Skin: excessive sweating
   Osmotic diuresis: glucose, urea, mannitol

3. Salt gain (Hypervolaemia)

a. Excessive sodium intake

Iatrogenic: IV NaHCO3, hypertonic saline

Salt ingestion: intentional, accidental, sea water immersion

b. Mineralocorticoid excess

Hyperaldosteronism

Cushing's syndrome

B. Clinical features

- Tremulousness, irritability, ataxia, spasticity, mental confusion, seizures and coma.
- The diagnosis would require an identification of the aetiological state

C. Treatment of hypernatraemia

- Depends on type of hydration, the cause, and the time period of development.
- Extracellular hypertonicity results in extraction of water from cells and causes cellular dehydration and shrinkage of organs including the brain. If the hypertonicity persists the brain will revert to its original volume due to the development of new osmotically active particles in the nerve cells, termed ***'idiogenic osmols'***. Thus, if a patient who has long standing hypernatraemia is infused with hypotonic fluids, there is a danger of much of the water ending up in the brain causing cerebral oedema. It is essential that hypertonically dehydrated patients have their extracellular hypertonicity lowered slowly.

1. Pure water depletion (Isovolaemia):

- Should be given water orally if tolerated.
- If not, set up an IV infusion of 5% DW or 0.45% Nacl. The volume and rate of infusion may be calculated as follows:

a. Calculation of volume required:

- ***Volume*** = Deficit + daily requirements + ongoing loses
- ***Deficit:***

  TBW(litres) = 0.6 x body weight (kg)

  $$\text{Desired TBW} = \frac{\text{TBW (current) x measured Na(mmol/L)}}{\text{Desired Na(mmol/L)}}$$

  Water deficit = Desired TBW(normal) - TBW(current)
- ***Daily requirements:*** allow one to two litres a day

b. Rate:

- Patients with hypertonicity, because of the possible development of idiogenic osmols, should have their hypertonicity resolved slowly.

- Roughly one half of the calculated water deficit + daily maintanance + ongoing loses can be administered in the first 24 hours, followed by correction of the remaining deficit over the next 1-2 days.
- The plasma osmolality should ***NOT*** be corrected at a rate greater than ***1mosm/kg/hour*** or the change in sodium concentration should not exceed 1mmol/L/hour.

 # Diabetes Insipidus

- ***Cranial:*** DDAVP intranasal 5-10ug once or twice daily or aqueous vasopressin SC 5-10 U twice daily.
- ***Nephrogenic:*** Thiazide diuretic with or without indomethacin + modest Na restriction

2. Hypotonic fluid depletion (hypovolaemia):

- The management of this conditon is similar to the above. In patients with significant extracellular volume depletion, the first priority is to restore the circulating volume as soon as possible with normal saline, blood, plasma or plasma expanders.
- Once the plasma volume is restored, and the blood pressure returned towards normal, the hypernatraemia is dealt with as outlined above.

3. Salt gain (hypervolaemia):

- The aim is to remove sodium rapidly using a potent diuretic (eg. iv frusemide) and at the same time 5% DW is infused.
- In severe and difficult cases dialysis may be necessary.

_ HYPONATRAEMIA

A. Causes

1. **Pseudohyponatraemia (normal plasma osmolality)**
   Hyperlipidaemia
   Hyperproteinaemia

2. **Hypertonic hyponatraemia (high plasma osmolality)**
   Hyperglycaemia

3. **Hypotonic hyponatraemia (low plasma osmolality)**
   - ***a. Hypovolaemia*** Water and Na depletion with depletion of Na being proportionally greater than water):
   - Extrarenal loss (urine Na < 20mmol/L)
     Diarrhoea, vomiting, excessive sweating
   - Renal loss (urine Na > 20mmol/L)
     Diuretics
     Osmotic diuresis - DM, mannitol
     Addison's disease
     Cerebral salt losing syndrome
     Salt-losing nephritis - Diuretic phase of ATN, post-obstructive, chronic renal insufficiency, type II RTA, medullary cystic disease, congenital polycysticdisease, chronic interstitial nephritis.
   - ***b. Isovolaemia*** (Found in patients whose kidneys have an inability to excrete electrolyte-free water, there is a normal, or slightly decreased extracellular sodium content, and a normal or slightly increased extracellular fluid volume):
   - Syndrome of inappropriate antidiuretic hormone (SIADH)
   - Abnormal ADH release
     Addison's disease
     Hypothyroidism
     Severe potassium depletion
     Stress
     Post-surgery
     Psychogenic
   - Drugs eg. Thiazides, chlorpropamide, carbamazepine.
   - Renal insuffiency
   - ***c. Hypervolaemia (***Dilutional hyponatraemia due to the renal retention of water being proportionally greater than the retention of sodium):
     Cardiac failure
     Cirrhosis of liver
     Nephrotic syndrome

B. Clinical features

1. The clinical features of ***acute hyponatraemia*** are related to osmotic water shift that leads to increased ICF volume and brain cell swelling.
- Mild hyponatraemia is usually asymptomatic.
- Serum Na of about 120 mmol/L may be associated with disturbed mental state, restlessness, confusion & irritability.
- As the Na approaches 110 mmol/L, seizures and coma may occur.

2. In ***chronic hyponatraemia***, adaptive mechanisms tend to minimize the increased in ICF volume & its symptoms.

C. Assessment and Investigations

- Assess the patient's fluid status from skin turgor, tonge moisture, BP, JVP, presence or absence of pulmonary oedema and fluid chart.
- Measure serum osmolarity and compare it to the calculated osmolarity - an increased in osmolar gap occurs with substance such as ethylene glycol, mannitol, hyperglycaemia etc.
- Urine Na combined with clinical assessment of fluid status may help determine the underlying cause:
  - Volume depletion from an extra-renal cause is normally associated with a low urinary Na (< 20 mmol/L).
  - Dehydration with a high urinary Na (>20mmol/L) suggests inappropriate renal salt-wasting.
  - Fluid overload with a low urine Na is seen in conditions such as CCF, cirrhosis or nephrotic syndrome.
  - Isovolaemia with a high urine Na is seen with SIADH.

D. Treatment of hyponatraemia

1. General principles:

- To normalize patient's extracellular volume and sodium concentration.
- If the plasma Na is >120mmol/L, agressive treatmant is not required.
- If the plasma Na is <120 mmol/L, correct it at a rate of less than 10 mmol/L per day (0.5-1 mmol/L/hour).
- If the plasma Na is <105 mmol/L, or the patient is symptomatic, urgent treatment is required with a more rapid rate of increase of 1-2 mmol/L/hour for the first 3-4 hours. However, the total daily increment in the plasma sodium should still not exceed 10 mmol/L.
- Avoid ***i) too rapid a correction to normonatraemic or hypernatraemic levels, and ii) development of hypernatraemia in the period following the original correction*** - may cause central pontine myelinolysis.
- Limit correction of serum sodium concentration to no higher than 130 to 135 mmol/l over the first 48 hours.
- Formulas:
  1. Osmolarity(mmol/L) = 2(Na + K) + BU + Glucose (all in mmol/L) [Normal: 270-295]

2. Na deficit = (Desired Na-measured serum Na) x0.6x BW(kg)
3. 3% Nacl provides 0.51 mmol/L of Na/ml
4. 0.9% Nacl provides 0.154 mmol/L of Na/ml
5. 1g of Nacl = 17 mmol/L

2. Hypervolaemic hyponatraemia:

- Retriction of Na & water intake, correction of hypokalaemia & promotion of water loss in excess of Na . This can be done with judicious use of diuretics with replacement of a proportion of the urinary Na loss to ensure net free water excretion.
- Treat aetiology.

3. Isovolaemic hyponatraemia:

a. No symptoms

- Strict fluid restriction (e.g. <500mL daily) until serum sodium rises.
- 0.9% saline with frusemide may also be used.

b. Symptomatic

- Rapidly increase the patient's extracellular tonity to prevent cerebral oedema and to decrease his extracellular volume (e.g. IV frusemide + hypertonic 3% saline).
- The principle here is to administer 3% saline at a rate equal to frusemide- or bumetanide-induced urinary electrolyte losses. The difference in the hourly rate of urine flow and hypertonic saline infusion will equal the net negative fluid balance.
- This approach avoids dangerous overexpansion of ECF and corrects primary cause of the hyponatraemia - excessive total body water.

Example

- To calculate the desired negative water balance:
  Weight = 60kg, serum Na = 115mmol/L
  Total body water (TBW) = 0.6 x 60 = 36 litres
  If desired serum Na = 125mmol/L
  then desired TBW = 115/125 X 36 = ~33 litres (formula as mentioned in hypernatraemia)
  Therefore, net negative water balance = (36-33) = 3 litres
- Choose the rate of correction based on clinical circumstances eg. 1 mmol/L. The total change in plasma Na (125 - serum Na) divided by rate of correction (1 mmol/l) will yield the period of time over which correction should occur eg. 10/1 = 10 hours.
- The negative water balance divided by the period of time calculated above yields the target rate of free water removal in liters/hour eg. 3 /10 = 0.3 liter/hour = 300 ml/hour.
- Establish urine output with IV frusemide 40mg and titrate dose to achieve a urine output (ml/hour) equal to the rate or free water removal ie 300 ml/hour.
- Na deficit (0.6 x [125 - Na] x 60) = 0.6 x[125 -115] x 60 = 360 mmol/L Nacl
- Replace with 3% Nacl = 360/0.51ml = 700 ml of 3% Nacl over 10 hours.

Alternatively

- If we infuse 3% saline at 100ml/hour and hourly urine flow is established at 500ml/hour with frusemide, a negative balance of 400mls per hour is achieved. We can thus achieve a 3 L negative water balance over 7.5 hours.
- Hourly serum and urinary electrolytes are mandatory.

3. Hypovolaemic hyponatraemia:

- Rehydration should be accomplished over 2 to 3 days (usually with normal saline).
- ***Amount*** of fluid to be given is calculated as below:
  i) ***Amount depleted:*** Calculate from degree of dehydration, e.g. mild = 5%, moderate 5-8%, severe = 8-12% = (%x BW [kg] x 1000) ml
  ii) ***Normal daily fluid requirement:*** Varies with patient size generally 1 to 2 litres
- ***Rate:*** As a rule of thumb,1/2 of calculated deficits + maintenance + projected losses may be given during the first 24h of treatment. About 1/2 of the total 24h volume is given in the first 8h.
- ***Type of fluid:*** usually normal saline

4. Syndrome of inappropriate ADH secretion (SIADH):

- ***Inclusive criteria*** for the diagnosis are:
  a. Plasma Na <130mmol/l.
  Plasma osmolality <275 mosmol/kg.
  Urine Na >20mmol/l.
  Urine osmolality > plasma osmalality.
  b. No oedema or signs of hypovolaemia.
  c. Normal renal, thyroid & adrenal fucntion.
  d. The patient should not be taking diuretics.
- ***Treatment*** - as in isovolaemic hyponatraemia but may also use demeclocycline or lithium.

_ HYPERCALCAEMIA

A. Causes

1. ***Excess PTH***
- Primary hyperparathyroidism
- Tertiary hyperparathyroidism
- Ectopic PTH secretion
- Multiple endocrine disorder

2. ***Malignant disease***
- Secondary deposits eg. breast, bronchus
- Haematological eg. myeloma, leukaemia

3. ***Excess action of vitamin D***
- Iatrogenic or self administered excess
- Sarcoidosis

4. ***Other endocrine disease***
- Thyrotoxicosis
- Addison's disease
- Acromegaly

5. ***Miscellaneous***
- 'Milk alkali' syndrome - excess calcium intake
- Drugs eg.Thiazides
- Long term immobility
- Familial hypocalciuric hypercalcaemia

B. Clinical Features

- ***Neurology*** - Depression, proximal myopathy, fatigue, confusion, stupor, and coma.
- ***Renal*** - Renal colic, haematuria, hypertension, polyuria and nocturia.
- ***Bones*** - bone pain, pathological fractures.
- ***Abdominal*** - Nausea, vomiting, constipation, abdominal colic, peptic ulcer disease, pancreatitis.
- ***General*** - soft tissue and corneal calcification.
- ***ECG changes*** - shortened QT interval.

C. Investigations

- Serum calcium, inorganic phosphate, intact PTH, FBC, BUSE, albumin, ALP, skeletal survey, bone scan, free T4, TSH, and other investigations as appropriate.

D. Treatment

I. Acute therapy

- Strategy: calcium level is initially reduced through dilution and increasing renal excretion. Reduced production is the longer term goal.
- Severe hypercalcaemia is defined as serum Ca > 14mg / dl (3.5mmol / l).
- Correct 0.8mg / dl up or down for each 1g / dl albumin down or up from baseline value 4.0g / dl . Add or subtract 0.02 mmol / l for every 1g / l of albumin below or above 40g / l.
- Acute therapy is warranted if severe symptoms are present or serum calcium is greater than 12mg / dl (3mmol / l).
- The first step is rehydration and saline diuresis. An inhibitor of bone resorption should be given early eg. pamidronate. Mitramycin can be used if pamidronate is not effective in malignant hypercalcemia. Calcitonin can be used in patients with renal failure or added to another drug to rapidly control severe hypercalcemia. In oliguric renal failure that cannot

be treated with IV saline, haemodialysis with a calcium-free dialysate lowers serum calcium temporarily.

- With rehydration, frusemide administration could help bring down serum calcium by a mean of 3mg / dl (0.75 mmol) over a 24 hour period.

1. Rehydration and saline diuresis:

- Severely hypercalcaemic patients are almost always dehydrated, and the step in therapy should be ECF restoration with 0.45-0.9% saline. Initial infusion rate should be about 300-500ml / hr and reduced when ECF volume deficit has been partially corrected. 3-4 litres may be required for the first 24 hrs. CVP monitoring may be required. Fluid balance and electrolytes must be carefully monitored. Potassium and magnesium supplements are needed (eg. to add 20mmol / L of K and 10mmol / L of Mg to each litre).
- When ECF volume is restored, infusion of 0.45-0.9% saline 3-6 litres a day for 2-3 days should be given to promote calcium excretion. Na+competitively inhibits the renal tubular reabsorption of Ca. IV ***frusemide*** 20-40mg 3-4 times a day is given to prevent overloading and to further promote Ca excretion.

2. Steroids *(effective in myeloma, other haematological malignancies, sarcoidosis, vit D excess; other tumours rarely respond):*

- Reduces intestinal absorption of Ca and inhibit osteolytic resorption.
- IV ***hydrocortisone*** 200 mg 6-8hrly or ***prednisolone*** 30-60mg daily.
- May take 5-10 days for se Ca to fall. After serum calcium stabilizes, the dose should be gradually reduced to the minimum needed to control symptoms of hypercalcaemia.
- Treat the underlying malignancy.

3. Calcitonin:

- Inhibits bone resorption and increases renal calcium excretion.
- Relatively weak agent. Has an acute but very short-lived hypocalcaemic action (few days). Safe in renal failure.
- 4-8IU / Kg IM or SC every 6-12 hourly up to 3 days (then tachyphylaxis occurs). The effect may be prolonged by concomitant therapy with prednisolone 30-60mg od.
- Recommended initial dose of calcitonin is 4IU / kg every 12 hours by SC or IM injection. If the response to this dose is not satisfactory after one or two days, the dose may be increased to 8IU / kg every 12 hours or maximum of 8IU / kg every 6 hours.

4. Mithramycin (Plicamycin):

- Useful in malignancy-related hypercalcaemia.
- Toxic to osteoblasts and inhibits bone resorption.

- IV10-25 mcg / kg in 500ml 5% dextrose water infused over 4-6hours. Effect lasts for 48-72 hrs. Monitor FBC, PT, LFT, se creatinine every 2-3 days. Can be repeated when hypercalcaemia recurs.
- Mitramycin is ***contraindicated*** in patients with a bleeding diasthesis and should be ***avoided*** in patients with renal failure or hepatic dysfunction, or during myelotoxic chemotherapy.

5. Bisphosphonates:

- Probably the treatment of choice in hypercalcaemia of malignancy and primary hyperparathyroidism.
- Inhibit bone resorption.
- ***Pamidronate*** - Single dose of 60-90mg in 1 litre of 0.9%saline or 5% DW is infused over 24 hrs.

  or

  Etidronate, 7.5mg / kg in 250 ml 0.9% saline, is infused IV over 2 hours daily until se Ca is normal or maximum of 7days. PO 400-1600mg per day maintenance may prevent reccurence.
- The action starts after several days and lasts for weeks to months. Treatment can be repeated if hypercalcemia recurs (usually after 2-3 weeks).
- Se creatinine should be monitored.

6. IV or oral phosphate is quickly effective, but rarely used as it is hazardous, precipitating calcium in soft tissues including the kidney.

7. Dialysis is quick and effective and is likely to be needed in severe cases or with renal failure.

II. Chronic management of hypercalcaemia

1. General measures:

- Be kept active, avoid immobilization, and drink adequate fluids.
- Avoid thiazide diuretics, large doses of vit D and A, calcium-containing antacids or supplements.
- Discontinuation or reduction in dosage of digitalis (hypercalcaemia potentiates toxicity).

2. Treatment of underlying cause:

a. Hyperparathyroidism:

- Surgical removal of adenoma, or total parathyroidectomy + implantation of half a gland in the sternomastoid / forearm for parathyroid hyperplasia associated with MEN syndrome.

b. Malignant hypercalcemia:

- General measures as mentioned above after acute management.
- IV pamidronate can be given when hypercalcemia recurs.
- Mithramycin may be used if pamidronate is ineffective.

- Prednisolone 30-60mg daily usually controls hypercalcemia in multiple myeloma and other haematological malignancies.
- Oral phosphate can be tried if the serum phosphorus level is low and renal function is normal.

c. Hypercalcemia due to other disorders:

- Vitamin D toxicity should be treated with prednisolone and a low calcium diet (<400mg / day). The effects of Vitamin D itself may take up 2 months to abate.
- Hypercalcemia due to sarcoidosis responds to prednisolone, and a dose of 10-20 mg / day may be sufficient for long-term control.

_ HYPOCALCAEMIA

A. Causes

1. Hypoparathyroidism

- Idiopathic hypoparathyroidism (Autoimmune)
- Congenital deficiency (DiGeorge's syndrome)
- After neck surgery
- Severe hypomagnesaemia (Bone resistance to PTH)

2. Resistance to PTH

- Pseudohypoparathyroidism

3. Vitamin D deficiency and resistance

- Deficient synthesis & supply of vitamin D.
- Impaired absorption of vitamin D.
- Chronic liver disease *(Failure of 25-hydroxylation of vitamin D.*
- Chronic renal failure*(Failure of 1-hydroxylation of 25(OH)D)*

- Vitamin D dependent rickets *(Failure of 1-hydroxylation of 25(OH)D)*
- Familial hypophosphataemic rickets (*vit D resistant rickets)*
- Miscellaneous: Anticonvulsant, renal tubular acidosis

4. Increased phosphate levels
- Chronic renal failure (high ionised form)
- Phosphate therapy

5. Drugs
- Calcitonin and bisphosphonates

6. Miscellaneous
- Acute pancreatitis
- Citrated blood in massive transfusion
- Hypoalbuminaemia
- Alkalosis

B. Clinical Features

- Paraesthesia
- Circumoral numbness
- Cramp
- Tetany
- Dystonia
- Convulsion
- Psychosis
- Chvostek's sign - gentle tapping over facial nerve causes twitching of facial muscles
- Trousseau's sign - inflation of the sphygmomanometer cuff above diastolic pressure for 5 min causes carpopaedal spasm.
- Papilloedema (severe)
- Prolonged Q-T interval on ECG

C. Investigations

- Se calcium - Low
- Phosphate level - High
- PTH levels - Absent or low
- Serum BU and creatinine
- Plasma magnesium
- Plasma albumin
- Vitamin D studies: 25-hydroxycholecalciferal , 1,25-dihydroxycholecalciferol

D. Management

1. Acute symptomatic hypocalcaemia:

- 10-20ml of 10% calcium gluconate (90mg of elemental calcium / 10mL) IV over 10 minutes followed by infusion of 10-50ml of ca gluconate in 500ml 5%DW or normal saline over 4-8hrs. Calcium chloride can also be used (360mg elemental calcium / 10mL).
- Avoid recurrent symptomatic hypocalcaemia and to maintain se calcium between 8-9mg / dl
- Hypomagnesaemia if present, must be treated.
- The underlying cause should be treated or long-term therapy started, and the IV infusion then gradually tapered.

2. Long term management:

a. Hypoparathyroidism and pseudohypoparathyroidism requires calcium supplements and vitamin D or its active metabolite.

- The goal is to correct symptomatic hypocalcaemia without inducing the development of hypercalcaemia (since PTH cannot limit urinary calcium excretion in these diseases, hypercalciuria and nephrolithiasis are potential side effects).
- The objective is to maintain serum calcium levels slightly below the normal range (bet 8-9mg / dl), with urinary calcium levels below approximately 250mg / day or 'spot' urine calcium of <30mg / dl.
- While the dose of vitamin D is being titrated, serum calcium should be measured twice a week. When a maintenance dose is achieved, serum and 24-hour urine calcium levels should be monitored every 3-6 months. If urine calcium exceeds 250mg / day, the dose of vitamin D should be reduced.
- If hypercalcaemia develops, vitamin D and calcium should be stopped until serum calcium falls to a normal concentration, then both should be restarted at lower doses.
- Symptomatic vitamin D-induced hypercalcaemia should be treated with prednisolone.

i Oral calcium supplements:

- The initial dose dosage is 1-2g elemental calcium PO tds during the transition from IV to oral therapy. For long term therapy, the typical dosage is 1-2g / d PO daily in divided doses with meals.
- Calcium carbonate contain 400mg elemental calcium / 1g (ie 40%) is the calcium of choice. Calcium lactate contain 130 mg elemental calcium / 1g (ie 13%).

ii Vitamin D:

- Therapy should be started as soon as oral calcium is begun.
- Various forms of vitamin D, non-active and active forms, are available. Active forms of vit D is much more expensive than vitamin D, but its lower risk of toxicity makes it the best choice for most patients.
- Non-active forms need to be 25-hydroxylated into more active forms in the liver, which are then 1α-hydroxylated in the kidney into the most active form.

a. D2 or ergocalciferol:

- Usually daily dose 25,000-150,000IU / day.

b. D3 or cholecalciferol:

- Requires weeks to achieve full effect.
- The initial dose is 50,000 IU (1.25mg) PO od, and usual maintenance doses are 50,000-100,000 IU PO od. The dose can be increased at 4-6 week intervals.

- Active forms:
  a. Calcitriol (1α-25-dihydroxycholecalciferol- active natural form of vit D):
  - The initial dose is 0.25mcg PO od, and most patients are maintained on 0.5-2.0mcg PO od.
  - The dose can be increased at 2-4 week intervals.

  b. Alfacalcidol (only requires hepatic 25-hydroxylation to become the active form):
  - The usual daily maintenance dose is 0.25-1mcg PO daily.

iii. Other measures:

- In patients with severe hyperphosphataemia, serum phosphorus should be lowered to <6.5mg / dl with oral phosphate binders before vitamin D is started.
- If hypercalciuria develops at serum calcium levels <8.5mg / dl, hydrochlorothiazide 50mg PO od, can be used to reduce urinary calcium excretion.

b. Vitamin D deficiency:

- Drugs of choice are ergocalciferol or cholecalciferol.

c. Chronic renal failure:

- Drugs of choice are calcitriol or alfacalcidol.

_ HYPERKALAEMIA

A. Causes

1. Decreased renal excretion:

- Renal failure: Acute or chronic
- Mineralocorticoid defiency:
  - Addison's disease
  - Hypoaldosteronism
- Drugs:
  - ACE inhibitors (usually with renal impairment)
  - Potassium sparing diuretics
  - NSAIDS
  - Cyclosporin therapy
  - Heparin therapy
- Acidosis

2 Increased potassium load:

- Potassium chloride: Iatrogenic and salt substitutes
- Potassium citrate
- Transfusion of stored blood
- Transfusion of irradiated blood

3. Increased release from cells:

a. Shift of K out of cells.

- Acidosis
- Insulin defiency eg. DKA
- Aldosterone deficiency
- ß-adrenoceptor antagonists
- Hyperkalaemic periodic paralysis

b. Tissue breakdown.

- Digoxin toxicity
- Rhabdomyolysis
- Tumour lysis
- Tissue necrosis/crush injury
- Succinylcholine
- Vigorous exercise (transient)

4. Pseudohyperkalaemia

- Increased in vitro release from abnormal cells
  - Thrombycytosis
  - Leucocytosis
- Haemolysis (commonly encountered)

B. Clinical Features

- Usually occur when K>6.5mmol/L
- Neuromuscular manifestations:
  Weakness, paraesthesia, areflexia, ascending paralysis.
- Cardiac manifestations:
  Bradycardia, prolongation of AV conduction, complete heart block, ventricular fibrillation and asystole.
- ECG changes:
  Tall tented T waves, small P wave, depressed ST segment, widened QRS complex, Sine wave (Biphasic wave, pre-cardiac arrest)

C. Acute Treatment

- Goals:
  - ***i) To protect the heart from the effects of K by antagonizing the effect on cardiac conduction (calcium).***
  - ***ii) To shift K from the ECF to ICF (Na bicarbonate, insulin and glucose).***
  - ***iii) To reduce total body K(Cation-exchange resin, and dialysis).***
- Treatment is urgent if the K is >6.5 mmol/L or ECG shows changes of hyperkalaemia.

Recommendations:

a. Mild to moderate hyperkalaemia (K 5.5-6.5 mmol/l) with no ECG changes:

- Low potassium diet.
- Stop drugs which may cause hyperkalaemia.
- Cation exchange-resins.
- Correction of acidosis in patient with metabolic acidosis.
- +/- Glucose and insulin infusion.

b. Severe hyperkalaemia (K >6.5 mmol/l) or with ECG changes:

- Immediate Calcium administration.
- Glucose and insulin infusion.
- Sodium bicarbonate infusion.
- Beta-agonist therapy.
- Dialysis.

1. Calcium administration:

- 10 ml of 10% ***calcium gluconate*** IV over 2-5 minutes. A second dose can be given after 5 mins if no change in the ECG is seen. Effect of calcium occurs within minutes and lasts for 1 hour.

- Slower infusion rates in patients on digitalis to avoid hypercalcaemia-induced digitalis toxicity.
- Calcium should not be given before or after bicarbonate in the same IV line to avoid precipitation.

2. Glucose and insulin infusion:
- Rapid acting ***insulin*** 10U + 50ml of ***50% dextrose*** IV infused over 30-60 mins (In patient with renal failure infuse insulin / glucose in the ratio of 1 unit of insulin to 8 gm of dextrose).
- Onset within 30-60 min and lasts for several hours.
- The above regimen can be repeated 6-8hrly.

3. Beta-agonist therapy:
- IV ***salbutamol*** 0.5mg IV in 15 mins or 10mg nebulization (with or without glucose and insulin infusion) has been shown to be effective in reducing K level (IV is preferred in patient with ESRD).
- If effective, the plasma K will fall by 0.5-1.5mg mmol / l in 15-30 mins & the effect will last for several hours.

4 Sodium bicarbonate infusion:
- IV infusion of ***bicarbonate*** 100-200 mmol / L over 30 min produces metabolic alkalosis which lowers ECF K.
- Onset of action occurs within 30 min and lasts for 1-2 hours.
- It is less effective in patients with renal failure.

5 Cation-exchange resins (Resonium A):
- Bind potassium in exchange for another cation in th GI tract, thereby removing K from body.
- Can be given orally (15-30g 3-4 times daily) or as enemas (30-60g in 200ml 3-4 times daily).

6. Haemodialysis or peritoneal dialysis when conservative measures have failed.

_ HYPOKALAEMIA

A. Causes

1. Reduced Intake.

2. Increased Excretion:

a. Increased renal excretion

- *Diuretics:*
  Thiazides
  Loop diuretics
- *Increased aldosterone secretion*
  Liver failure
  Heart failure
  Nephrotic Syndrome
  Conn's syndrome
  ACTH-producing tumours
- *Exogenous mineralocorticoid*
  Corticosteroids
  Carbenoxolone
  Liquorice
- *Renal tubular acidosis type 1 or 2*
- *Renal tubular damage*
  Acute leukaemia
  Cytotoxic treatment
  Nephotoxicity eg. amphotericin, aminoglycosides, penicillins.
- *Bartter's syndrome, Liddle's syndrome.*
- *Hypomagnesaemia.*

b. Gastrointestinal losses:
Vomiting
Severe diarrhoea
Purgative abuse
Villous adenoma
Ileostomy or uterosigmoidostomy
Fistula

3. Redistribution into cells:
Beta-adrenergic stimulation eg. AMI, Beta-agonists
Insulin treatment eg. DKA
Exogenous glucose
Alkalosis
Hypokalaemic periodic paralysis

4. Pseudohypokalaemia:
Leucocytosis.

B. Clinical features

- Usually present when K<2.5mmol/L
- Malaise, fatigue
- Neuromuscular disturbances:
  Weakness, hyporeflexia, paraesthesias, cramps, restless legs syndrome, rhabdomyolysis, paralysis
- Gastrointestinal : constipation, ileus
- Arrhythmias
- Polyuria, polydipsia, metabolic alkalosis
- ECG changes:
  Small or inverted T waves
  Prominent U wave
  Depressed ST segment
  Prolonged PR interval**.**

C. Important facts

- One gram of KCl contains 14mmol/l (14 mEq/l) of K.
- If serum K level does not appreciably rise after adequate K therapy (eg 72-96 hours after oral therapy), concomitant magnesium depletion should be suspected.
- In a patient with hypokalaemia and with low urinary potassium excretion (<20 mmol/l), hypokalaemia of extrarenal origin should be suspected.
- In asymptomatic patients with K of between 3-4 mmol/l who are vulnerable to cardiac arrhythmias eg. CCF, on digoxin, history of MI or IHD, potassium supplements are recommended.
- If potassium level is < 3 mmol/l, potassium supplement should be given to all patients.
- KCl is the preparation of choice in most patients except in those with metabolic acidosis, in which potassium bicarbonate or potassium citrate is preferable.

D. Management of hypokalaemia

1. Oral therapy:

- Method of choice for ***mild to moderate depletion (plasma K >2.5mmol/L).***
- Oral ***potassium chloride*** 1 to 2 gm every 2 to 4 hourly until return of serum potassium to at least 3.5 mmol/L.
- Potassium can also be given as ***slow-release potassium*** (1 tab= 8mmol/L) or ***effervescent potassium*** (1tab=14mmol/L) or ***liquid forms (***Liquid or effervescent preparations are preferred since slow release potassium has been shown to be associated with gastric erosion and because of its slow release nature is less efficacious in correcting more severe degrees of hypokalaemia).
- 40-200 mmol/l daily of potassium chloride may be required over periods of days or weeks eg. 20-40 mmol/L 2 to 4X daily depending on the severity of the depletion (as frequent as 2-4 hourly may be required).
- Monitor K levels closely to prevent hyperkalaemia.
- The ***potassium-sparing diuretics*** may be an alternative for patients in whom hypokalemia develops secondary to renal losses.

2. IV therapy:

a. Method of choice in patients with ***severe hypokalaemia(<2.5mmol/L), who are not able to take orally, with ECG changes and who are symptomatic*** eg cardiac arrhythmias with rapid ventricular response, familial periodic paralysis, and severe myopathy.

b. In ***asymptomatic patients*** without ECG changes, K should be given as follows:

- At a concentration less than 40mmol/L (<3g KCl in 1L of carrier fluid).
- At a rate of < 20mmol/h (10mmol KCl per hour recommended).
- The plasma K should be monitored regularly, and with ECG monitoring.

c. In ***emergency*** eg. cardiac arrhythmias, severe myopathy, K can be given at rates up to 40mmol/hr and in concentrations of 200-400mmol/l (by mixing 20-40 mmol KCL in 100cc of saline).

- Preferrably the fluid should be dextrose free as fast infusion of dextrose would result in endogenous insulin secretion, thus simulating an insuline/glucose infusion.

3. As soon as the ECG changes normalizes , cardiac rhythm returns to normal or respiratory muscle strength has been restored to normal, IV infusion is gradually tapered and then discontinued. Oral KCl is then initiated.

_ METABOLIC ACIDOSIS

A. Causes

1. High anion gap metabolic acidosis

a. Renal failure:

- Acute, chronic

b. Ketoacidosis:

- Diabetes mellitus, ethanol, starvation

c. Lactic acidosis:

(i) Type A (tissue hypoxia apparent):

- Severe hypoxia, severe anaemia, shock/haemorrhage, CCF

(ii) Type B (tissue hypoxia not apparent):

- Acquired disease: diabetes mellitus, liver failure, convulsions, tumours.
- Drugs/toxins: biguanides, ethanol, methanol
- Congenital disorders: G6PD deficiency, fructose 1,6 diphosphatase deficiency.

d. Toxin:

- Salicylate, ethanol, methanol, paraldehyde, ethylene glycol

2. Normal anion gap metabolic acidosis

a. Hyperkalaemic:

- Early uraemic acidosis
- Obstructive uropathy
- Renal tubular acidosis Type 4: Mineralocorticoid deficiency, tubule unresponsiveness.
- Ingestions/infusions: HCL, lysine/arginine HCL, ammonium chloride
- Diabetic ketoacidosis: post-therapy

b. Hypokalaemic:

- Renal tubular acidosis: Type 1 & 2
- Carbonic anhydrase inhibitor: acetazolamide
- Urine diversions: ureterosignoidostomy, vesico-colic fistula, obstructed ileal bladder
- Post-hypocapnic acidosis
- Acute diarrhoea.

Anion Gap = [K] + [Na] - [Cl] - [HCO3] (all in mmol/L)
The normal range is 8-16 mmol/L

B. Treatment of acute metabolic acidosis

- Treatment is aimed at the underlying disorder, such as insulin and fluid therapy for diabetes and appropriate volume resuscitation to restore tissue perfusion.
- The use of ***supplemental HCO3*** is indicated for treatment of ***hyperkalaemia and some forms of normal anion gap acidosis*** but has been controversial for treatment of increased anion gap metabolic acidosis.
- HCO3 therapy should probably not be used if the metabolic acidosis is associated with hypoxia but is most likely beneficial if the metabolic acidosis is secondary to GI HCO3 loss or renal tubular acidosis.
- Metabolic acidosis of PH <7.2 or NaHCO3 <8-10mmol/l should probably be treated with NaHCO3 (in the absence of hypoxia). A rough estimation of the amount required can be calculated from the following formula:

  0.5 X Body weight (kg) X Base deficit

  # Base deficit = 24 - Actual HCO3.
  # 1ml of 8.4% NaHCO3 provides 1 mmol/l of NaHCO3.
- In practice the patient is usually 'titrated' by slowly infusing bicarbonate and regularly checking the plasma (HCO3).
- Except in cases of extreme acidaemia, sodium bicarbonate should be dispensed as infusion (over a period of several minutes to a few hours) rather than a bolus.
- About 30 minutes must elapse after the infusion of bicarbonate is completed before its clinical effect can be judged.
- No further bicarbonate therapy should be given once the PH _ 7.2.
- Complications are (i) sodium overload (ii) hypokalaemia (iii) tetany (iv) 'overshoot' alkalosis.
- Potassium supplement should be started if the serum potassium concentration begins to fall during correction of the acidosis.
- Alkali therapy can lead to extracellular-fluid volume overload, especially in patients with congestive heart failure or renal failure. Administration of loop diuretics may prevent or treat this complication. If adequate diuresis can not be established, haemofiltration or dialysis may be required.

7. HAEMATOLOGY

_ IMMUNE THROMBOCYTOPAENIC PURPURA

- A relatively common disorder, particularly in women aged 15 - 50 years (Male : Female ratio is 1:3).
- Usually idiopathic (thus a diagnosis by exclusion) but may be seen in association with other diseases, eg. SLE, CLL, Hodgkin's disease, AIHA etc.
- It is due to platelet sensitisation with auto-antibodies (usually IgG) which results in their premature removal from the circulation by cells of the reticulo-endothelial system.

A. Clininal Features

- Insidious onset of petechial haemorrhage, easy bruising and in women, menorrhagia. Spleen is palpable in only 10% of cases.

B. Investigations

- ***Platelet count*** is usually 10 - 50 x 10^9 / L (10,000-50,000 / ul).
- ***Blood film*** shows reduced numbers of platelets, those present often being large.
- Antiplatelet IgG test is not only cumbersome and time-consuming, but has many false-positive and false-negative results.
- ***Bone marrow aspiration*** shows a normal reactive picture with an increased number of megakaryocytes. This is a test of exclusion rather than confirmation ie. exclusion of other causes (ITP is diagnosed only if the marrow is normal).
- ***Tests to exclude underlying aetiologies*** as mentioned above include: ANF, LE cells, RF, peripheral blood film, Coomb`s test (Evan`s syndrome), HIV serology.

C. Management of Chronic ITP

- Spontaneous remissions of chronic ITP are rare (10 – 15%); however, complete or partial remissions in response to treatment with glucocorticoids or splenectomy occur in most patients.

I. Therapy for patients with platelet counts >30,000/ul

1. Specific treatment (splenectomy or chronic therapy) may not be necessary in patients who have pletelet count of > 30,000 / ul. They generally have few symptoms, and remain stable over many years.

2. Brief courses of prednisolone may be used to raise the platelet count (to more than 50,000/ul) for dental work and surgery.

II. Therapy for patients with platelet counts <30,000/ul

_ INITIAL THERAPY

- Patients are treated initially with prednisolone; if there is no response or relapse occurs on tapering of the prednisolone, splenectomy is indicated.

1. Glucocorticoids:

- ***Prednisolone*** 40 - 60mg daily (or 1 - 2mg/kg daily - start with 1mg/kg and increase to 1.5 - 2mg/kg for non responders after 2 – 3 weeks) given for 4 - 6 weeks or until remission occurs. In the majority of patients, the platelet count rises in 3– 7 days. The steroid can then be tapered to maintain the platelet count over 30,000/ul (eg. decrease by 20 mg/day every week until 40 mg/day; then decrease by 10 mg/day every week until 20 mg/day; then decrease by 5 mg/day every week until off drug).
- Selected patients with severe thrombocytopenia and active bleeding may benefit from initial treatment with ***methylprednisolone*** 500-1000mg IV daily for 3 days, followed by prednisolone.
- 20% of patients have a complete remission and require no further treatment.
- 20% of patients fail to respond to steroids at all.
- 60% have a partial response, and half of these have little bleeding associated with mild or moderate thrombocytopenia (20,000-100,000/ul) and may require only small doses of steroid, (eg. prednisolone 5-15mg daily), or no further treatment. The other half of the partial responders eventually relapse and require splenectomy.

2. Splenectomy:

- Should be considered in patients who ***(i) fail to respond to steroids (still requiring steroid after 3 months or requiring prednisolone of more than 20mg/day to maintain platelet above 30,000/ul or failing to respond to prednisolone 2mg/kg/day within 3 weeks) (ii) develop serious glucocorticoid toxicity (iii) develop recurrent thrombocytopenia when glucocortocoids are tapered (good responders) (iv) are non compliant but responsive to steroid.***
- Prednisolone or gamma-globulin should be given preoperatively to raise the platelet count >50,000/ul.
- If the patient fails to respond to either of these measures and has platelet count of <50,000/ul, a platelet transfusion, 2 units/10kg may be given at the time of intubation for anaesthesia.

- Glucocorticoids should be tapered off slowly following splenectomy.
- At least two-thirds of patients with chronic ITP will achieve sustained remissions following splenectomy.

Good responders are those who respond to steroid/Ig. Splenectomy does not benefit when ITP is associated with other autoimmune disorders eg SLE.

Management of Splenectomy patient:

1. Avoid splenectomy if possible in children esp if < 5 years. If done, prophylactic oral penicillin V until adulthood.
2. In adult, antibiotic should be given for 5 years. Dosage, Pen V 500mg bd or amoxycillin 500mg OD.
3. Vaccination:

- All patients should be given **pneumococcal vaccine** (Pneumovax II) 0.5ml SC or IM. It should be given two weeks before an elective splenectomy. If the spleen is removed in an emergency, patients should, ideally, be vaccinated two weeks after the operation. Asplenic patients should have booster doses at 5-10 year intervals.
- **Hib vaccine (H. influenzae b)** & **Meningococcal Groups A and C vaccine** are also recommended for all patients at the same time as pneumocococcal immunisation.

_ **REFRACTORY CASES**

3. Danazol:

- Danazol has been recommended, in patients with thrombocytopenia which is unresponsive to steroids and/or splenectomy and with plaletlets count 30,000-50,000/ul with symptoms.
- ***Dosage*** is 200mg tds orally with prednisolone 1mg/kg/day. Taper the prednisolone when the platelet reaches safe levels or after 6 weeks. The danazol should be continued for at least 4-6 months before it is abandoned. If the platelet becomes normal, continue danazol at full dose for 6 months and then taper by 200mg per day every 3 months to the lowest dose allowing safe platelet counts (tapering can start at 3 months in a good responder).
- Responses are less frequent in patients less than 45 years of age.

4. Immunosuppressive therapy:

- Should be considered in patients who remain profoundly thrombocytopenic following splenectomy.
- Examples of agents used and regimens:
  - # ***Vincristine*** 1-2mg IV weekly for 4-6 weeks. Stop if there is no response after the 2nd dose. Do not give more than 4-6 doses, or peripheral neuropathy may occur.
  - # ***Cyclophosphamide*** 1-2mg/kg orally daily for 2-3 months; adjust the dose if neutropenia occurs. If a complete response occurs, continue at the full dose for 3 months and then stop the drug. If no response occurs within 8 weeks, stop the drug.
  - # ***Azathioprine*** 2-3mg/kg/d (response often occurs slowly). If a complete response occurs, continue at full doses for 18 months, and then stop treatment. If no response occurs in 6 months, stop treatment.

Pulse IV cyclophosphamide - Give 1g/m^2 iv every 4 weeks for a total of 4 courses.

5. Immune globulin:

- Immune globulin is reserved for patients with severe haemorrhage, those undergoing surgical procedures, or prior to delivery. It may also induce remission in 5% of patients.
- 0.4g/kg IV daily for 5 days, or 1g/kg IV daily for 2 days, produces a rapid but temporary increase (1-6 weeks) in the platelet count and may prolong the survival of transfused platelets.

6. Platelet transfusions:

- Platelet transfusions are generally contraindicated in ITP.
- May be beneficial in patients with acute, life-threatening bleeding or if the platelet count is less than 10,000/ul. It may raise the platelet count immediately, but the count generally returns to baseline 24 hours later. Transfusion should be repeated until the bleeding is controlled by specific treatment or stopped spontaneously.

 # The reliable agents for obtaining short-term but generally transient responses are IV gamma globulin and vincristine.

 # Danazol and cyclophosphamide are the most reliable single oral agents for producing durable improvement in the platelet counts.

- In the ***absence of CNS bleeding***, IV IG or IV methylprednisolone 1g over 30 min for 3 days (start prednisolone as usual) may be given with or without platelet transfusion.
- In the ***presence of CNS bleeding,*** IV methylprednisolone + IV IG + platelet transfusion (10U) (+/- neurosurgery as indicated) can be given.
- In the ***presence of posterior compartment bleeding,*** splenectomy followed by craniotomy + IV IG and platelet transfusion may need to be given.

HAEMOPHILIA

I. Haemophilia A

- This is an X-linked recessive disorder of deficiency of factors VIII:C (33% due to spontaneous mutation), and with rare exceptions afflicts males. The level of factor VIII:vWF is normal.

A. Clinical Features

- The clinical features depend on the level of factor VIII:C and corrrelation of coagulation factor activity and disease severity is as follows:

Coagulation factor activity (% of normal)	**Clinical manifestations**
< 1	Severe disease. Frequent spontaneous bleeding episodes from early life. Joint deformity and crippling if not adequately treated.
1 - 5	Moderate disease. Post traumatic bleeding (mild trauma). Occasional spontaneous episodes.
5 - 20	Mild disease. Post-traumatic bleeding (eg. after surgery or severe trauma).

- About two thirds of patients have moderate to severe disease. The joints involved in descending order of frequency are knees, elbows, ankles, shoulders, wrists and hips. The soft tissues involved in descending order of frequency are calves, thighs, buttocks and forearms.

B. Laboratory Features

* ***The normal values for VIII:C range from 50 – 200%.***

- ***Bleeding time*** - normal.
- ***PT*** - normal.
- ***aPTT*** - prolonged (may be normal in mild cases)
- ***Clotting time -*** prolonged in severe cases.
- Reduced ***factor VIII*** assays.

C. Management

1. Mode of treatment in Factor VIII deficiency:

a. Factor replacement therapy:

- The dosage of replacement therapy is determined by the nature of bleeding and the severity of the haemophilia. One unit of clotting factor is the amount contained in the equivalent of 1 ml of fresh plasma with 100% clotting activity. Plasma volume is estimated as 50ml/kg body weight. The replacement dose of factor VIII can be calculated as follows:

  Dose(U) = (desired % activity - initial % activity) X wt in kg X 0.5

- The circulating half life of Factor VIII is 8-12 hrs. Efficient replacement therapy requires serial transfusion every 8-12 hr.
    1. ***Fresh-frozen plasma (FFP)*** contains all the coagulation factors in nearly normal concentrations. One ml of FFP will provide approximately 0.5 U of factor VIII. However, unless plasma exchange is done, sufficient whole plasma cannot be given to patients with severe haemophilia to raise factor VIII to levels that effectively prevent or control bleeding episodes.
    2. ***Cryoprecipitate*** contains factor VIII, vWF and fibrinogen. The concentration of factor VIII is approximately 100U / bag (or 3-5 U per ml).
    3. ***Lyophilized factor VIII concentrate*** is purified from plasma pooled from 2,000-30,000 donors. Factor VIII concentrate is the preferred therapy for most patients with severe haemophilia. It is packaged in bottles supplying 250-1000 units of factor VIII.
    4. ***Monoclonal purified or Recombinant factor VIII*** are also available and may be preferred to minimize viral infections and exposure to irrelevant proteins.

b. Non-blood products:

1. ***DDAVP (desmopressin)*** IV produces a rise in factor VIII proportional (2-3 X) to the initial level of factor VIII. It is useful for treatment of bleeding episodes in mild haemophiliacs and as prophylaxis before minor surgery. Repeat doses may be fully effective only when given about 48 hours later because of tachyphylaxis. The side effects include hyponatraemia and water intoxication. It cannot be substituted for factor replacement therapy in patients with life-threatening bleeding or severe factor VIII deficiency.
2. ***Epsilon-aminocaproic acid (EACA) and Tranexamic acid:*** these are antifibrinolytic agents and can be used to help control mucous membrane bleeding (eg. epistaxis, menorrhagia and dental surgery). They are contraindicated in haematuria.

2. Treatment and prevention of bleeding:

a. General measures:

- DO NOT ADMINISTER IM INJECTIONS.
- Avoid aspirin or NSAIDs.
- Start therapy as soon as possible (even on patients suggestion).
- Educate patient.
- Immobilize joint and advise rest.

b. Replacement of factor VIII deficiency:

1. ***Minor bleeding such as superficial abrasions and ecchymoses, early haemarthrosis, early muscle bleeding, nose and gingival bleeding and minor haematuria can be managed with:***

- ***Desmopressin acetate,*** 0.3ug/kg IV in 50ml saline over 20 min or nasal spray 300ug repeated at 12-24 hours intervals as necessary.
- Alternately with one to two infusions of ***cryoprecipitate or factor VIII concentrate*** sufficient to raise the factor VIII level to***20-30%.***

2. ***Definite or threatening severe haemorrhage:***

- Complicated haemarthroses, expanding soft-tissue haematomas, head injury without neurological abnormality, severe trauma without evidence of bleeding , minor GI haemorrhage and minor surgery can be treated by giving a dose of ***factor VIII concentrate*** calculated to acheive a factor VIII activity of about ***30-50%*** normal and the same dose should then be repeated 8-12 hourly; for joint bleeding 1-2 days, for minor GI bleed 2-3 days, for moderate GI bleed 7-10 days and for gastric ulcer until resolved.

3. ***Life-threatening haemorrhage:***

- Major trauma with bleeding, potential airway obstruction due to retropharyngeal bleeding, retroperitoneal bleeding, massive GI bleeding, and intracranial haemorrhage require a dose of ***factor VIII*** that will achieve about ***100%*** of the normal acitvity followed by half of the initial dose every 8hrly for 1-2 days and then every 12 hrly for 3-5 days after cessation of bleeding or a total duration of about 7-14 days.

4. ***Major Surgery:***

- For major surgical procedures, a dose of ***factor VIII concentrate*** sufficient to achieve a level ***80-100%*** of normal should be given an hour prior to surgery. A second dose, half the initial dose, should be given 5 hours after the first dose, then 8-12 hrly for 1-2 days and 12 hrly thereafter for a period of 10-14 days postoperatively.

5. ***Dental procedures:***

- Haemophiliacs prior to minor dental procedures can be managed by a single infusion of ***cryoprecipitate or factor VIII concentrate*** (to ***30%*** normal activity) coupled with the administration of antifibrinolytic agent eg. ***EACA*** 4-6g qid or ***tranexamic acid*** 500mg 3-4x/day for 7 to 10 days.

 # Factor VIII levels need to be determined every 2-3 days and the dose of Factor VIII adjusted accordingly.

II. Haemophilia B (Christmas disease)

- It is caused by a deficiency of factor IX.
- The inheritance and clinical features are identical to haemophilia A. The two disorders can only be distinguished by specific coagulation factor assays.
- Treatment of factor IX deficiency is by either ***FFP, prothrombin-complex concentrate or factor IX concentrate.***
- Dosage is calculated as below:

  Dose(U) = (desired % activity-initial % activity) X wt in kg

- Compared to factor VIII, note that a larger volume of factor IX is required due to larger volume of factor IX that diffuses into the extravascular tissues.
- Factor IX has a half-life of about 24 hours, therefore the appropriate dosage interval for factor IX is ***18-24 hours.***
- Desired levels of factor IX will depend on the severity of bleeding and the clinical indications as in haemophilia A.
- Desmopressin and cryoprecipitate are ineffective.

_ ANTICOAGULATION THERAPY

A. Relative Contraindications To Anticoagulant Therapy

\# *Prior to the initiation of anticoagulant therapy, patients must be screened for the presence of relative contraindications to therapy.*

_ ***Contraindications to anticoagulant therapy are:***

- Active bleeding (eg. peptic ulcer disease).
- Bleeding tendency (eg. haemophilia, thrombocytopenia).
- Uncontrolled hypertension (systolic > 180 mmHg).
- Intracranial haemorrhage or stroke within 2 weeks.
- Recent surgery or invasive procedures within 2 weeks.
- Pericarditis or pericardial effusion.
- Severe trauma within 2 weeks.
- Pregnancy (mainly for warfarin in early pregnancy and towards delivery).
- Unsatisfactory compliance, elderly or debilitated patients.

- Severe liver diseases – acute or chronic.
- Aortic dissection

B. Heparin

- Heparin is a mixture of polysaccharide chains with molecular weight from 3000 to 30000.
- Direct acting anticoagulants by potentiating the activity of antithrombin III to inactivate coagulation factors including thrombin and factor Xa.
- Produces prolongation of TT and aPTT.
- Half-life in the circulation is about 60-90 minutes but is prolonged in patients with severe liver disease. Heparin does not cross the placenta.

1. Dose:

a. Treatment of established thrombosis:

- Loading dose of 5000 U as a bolus injection, followed by 1,000 U/hour delivered by continuous IV infusion (eg. 25,000U of heparin in 500ml of D5%).
- The aPTT should be measured prior to starting heparin therapy and q4-6h during adjustment of infusion rate. aPTT of 1.5-2.5 times the upper limit of control is considered therapeutic (Normal 25-35 seconds). When the heparin clearance stabilizes, the aPTT can be determined daily.
- The maintenance dose can be adjusted as in the table below:

PTT results (seconds)	Dosage adjustment	Time of repeat PTT
<50	Give 5000 unit bolus and increase infusion by 100u/hr	Repeat in 6 hours
50-59	Increase infusion by 100u/hr	Repeat in 6 hours
60-85	No change	Repeat next morning
86-95	decrease infusion by 100u/hr	Repeat in 6 hours
96-120	Stop infusion for 30 mins and decrease infusion by 100u/hr	Repeat in 6 hours
>120	Stop infusion for 60 mins and decrease infusion rate by 200u/hr	Repeat in 6 hours

The above table is referred to when PTT is prolonged without bleeding. In the presence of bleeding, the heparin infusion should be stopped and consideration made to revert the action of heparin.

- More recently, heparin therapy has been recommended based on the patient's weight. The bolus dose is 80 U/kg , then 18 U/kg/hour as maintenance. With this regime a greater percentage of patients achieved the therapeutic threshold within 24 hours compared to those patients treated in the standard fashion.

- Alternately, adjusted-dose subcutaneous administration can be given but control is less even. The heparin dosage is adjusted to achieve a mid-dose aPTT (measured 6 hrs after administration) of 1.5-2.0 times the control value. A dosage of 7,500-15,000 U SC q12h is usually necessary.
- Patients should be started on oral anticoagulants (eg.warfarin) to achieve appropriate prolongation of the PT, and heparin is then discontinued, and patients are then maintained on warfarin. The usual duration of combined heparin-warfarin therapy is 3-7 days.

b. Prevention of deep vein thrombosis:

- 5000U SC 8 or 12 hrly, or in pregnancy 10,000 U every 12h.
- Monitoring is not required as these doses do not alter the aPTT.

2. Adverse effects:

- These include bleeding, thrombocytopenia (HIT), osteoporosis (long term therapy), and hypersensitivity reactions.

3. Reversal of heparin:

- Heparin effects wear off so rapidly that an antagonist is seldom required.
- When antagonism is needed, ***Protamine sulfate*** can be given by slow IV injection, in doses not more than 50mg over 10min. 1mg of protamine sulfate will neutralize about 100U of heparin. If given 30-60min after bolus injection, about 0.5mg of protamine sulfate will be required for every 100U of heparin. If heparin is given by continuous infusion, the dose of protamine sulfate should be calculated to neutralize approximately half of the preceding hourly dose of heparin. Effect of protamine can be measured by aPTT. If several hours have passed after SC injection, begin with small doses (5-10mg) and titirate according to PTT response.

C. Low molecular weight heparin

- LMWH is obtained from depolymerization of standard heparin to yield chains of molecular weight between 4000 to 6000 only.
- It inactivates factor Xa (free as well as platelet-bound), has a more favourable bioavailability and pharmacokinetics, as well as binds less avidly to tissue and plasma proteins.
- Its half-life is 2-4 times longer than unfractionated heparin and produces a more predictable response; hence, it can be administered once or twice a day in a fixed dose regime without aPTT monitoring.
- It resists inhibition by platelet factor 4, has less pronounced effects on thrombocytopaenia as well as platelet function and vascular permeability.
- It has been shown to be at least as effective and safe as unfractionated heparin in the treatment of deep vein thrombosis and has the added advantage of potentially able to be given as an outpatient management.

- It can also be used in pregnant women and probably caues less bleeding and osteoporosis.
- The application of these agents has now been extended to the treatment of acute coronary syndrome.
- There are many different types of LMWH in the market; the doage and dosing interval will depend on which agent is being used; eg. dalteparin, enoxaparin, nadroparin, reviparin, etc.

D. Warfarin:

- It Inhibits synthesis of vitamin K-dependent clotting factors, ie. Factor II, VII, IX and X. It also reduces protein C levels (short half-life of 6-8 hours). Thus, during the early stages of warfarin therapy, a hypercoagulable state may exist. Hence, heparin therapy should overlap over 3-7 days after the start of warfarin.
- Monitoring of therapy is by the prothrombin time (PT) and international normalized ratio (INR).
- The PT/INR reflects the warfarin dose given 24-48 hours earlier.
- Always measure baseline INR before initiating warfarin therapy as patients with underlying liver disease may have a pretreatment INR _ 1.4.
- Follow a tried and tested induction regime with daily meassurements of INR for the first week to prevent excessive anticoagulation.
- A decision about the duration of therapy should be made at the beginning:
    - single DVT or PE: 3-6 months
    - second DVT or PE: 1 year (some authors recommend life long)
    - more than twice: life long
    - atrial fibrillation: life long
    - those patients with obvious risk factors: to anticoagulate for as long as the risk factors are present
- Most serious bleeding occurs in the first month or so; thereafter, risk of bleeding is low if the INR is kept within the therapeutic range.
- Patients should be given verbal and written information regarding the implications of receiving warfarin. A list of foods and drugs that may in some way interact with warfarin should be given to the patients. They should be told what to do if there is uncontrolled bleeding.

1. Dose:

- Warfarin is usually initiated as 5mg daily for 2-3 days, subsequent daily doses are adjusted until the PT stabilizes in the therapeutic range.
- Alternately, Warfarin can be given as below:

Day	INR (0900 – 1000)	Warfarin dose (mg) (1700 – 1800)
1	<1.4	10
2	<1.8	10
	1.8	1.0
	>1.8	0.5
3	<2.0	10
	2.0-2.1	5.0
	2.2-2.3	4.5
	2.4-2.5	4.0
	2.6-2.7	3.5
	2.8-2.9	3.0
	3.0-3.1	2.5
	3.2-3.3	2.0
	3.4	1.5
	3.5	1.0
	3.6-4.0	0.5
	>4.0	Nil
		Predicted maintenance dose

4	<1.4	>8.0
	1.4	8.0
	1.5	7.5
	1.6-1.7	7.0
	1.8	6.5
	1.9	6.0
	2.0-2.1	5.5
	2.2-2.3	5.0
	2.4-2.6	4.5
	2.7-3.0	4.0
	3.1-3.5	3.5
	3.6-4.0	3.0
	4.1-4.5	Miss out next day's dose and then give 2 mg
	>4.5	Miss out 2 day's dose and then give 1 mg

- Recommended therapeutic ranges for oral anticoagulation.

Clinical state	***INR***
Venous thromboembolism	2.0-3.0
Atrial fibrillation	2.0-3.0
Post-myocardial infarction	2.5-3.5
Mechanical heart valves	2.5-3.5
Bioprosthetic heart valves	2.0-3.0 for 3/12
Recurrent systemic embolism	3.0-4.0

- When the dose for an individual is stable, the INR needs to be measured weekly for 2-3 weeks, then 2-3 weeks later, then every 6-8 weeks (up to 12 weeks). Maintenance dose is usually 2-10mg/day.

2. Adverse effects:

- These include bleeding, skin necrosis (in patient with protein C deficiency), fetal abnormalities if taken during pregnancy , and purple toe syndrome (due to cholesterol embolization).

3. Reversal of warfarin anticoagulation:

a. Life threatening haemorrhage: immediately give vit K 5-10mg by slow IV (vitamin K will reverse bleeding within 12-24 hours) and followed by FFP 2-4 U IV (the patient will be rendered refractory to oral anticoagulant, but not to heparin, for about 2 weeks). These may be repeated if necessary, depending on the INR and clinical condition of the patient.

b. ***Less severe haemorrhage, eg. haematuria or epistaxis:*** Withhold warfarin for 1 or more days and consider giving FFP or/and vitamin K 2-4mg IV or oral.

c. ***Insignificant/no haemorrhage but INR is above therapeutic range:***

If urgent invasive procedures (surgery/dental) are required, withold warfarin and vit K 2 - 4 mg orally +/- FFP can be given. INR reduction will occur in 24 hours. If the INR remains high, another 1 - 2 mg vit K can be given orally.

If urgent invasive procedures (surgery/dental) are NOT required and INR is above therapeutic range but ***< 5,*** omit the next dose and then resume warfarin at a lower dose when INR approaches the desired range.

If INR is between ***5 – 9,*** omit 2 doses of warfarin and repeat INR daily till it is in therapeutic range and then reinstitute warfarin at a lower dose. However, if the patient is at high risk of bleeding, vit K 2.5 mg orally can be given.

If INR ***> 9***, withold warfarin and give vit K 5 mg orally +/- FFP and repeat INR daily. INR will reduce in 48 hours. Vit K can be repeated if necessary.

 # it has been noted that the above regimes do not affect resumption of oral anticoagulation.

E. Anticoagulations and surgery

- The risk of increased bleeding during a procedure performed with a patient receiving antithrombotic therapy has to be weighed against the increased risk of a thromboembolism caused by stopping the therapy. The risk of stopping warfarin can be estimated and is relatively slight if the drug is witheld for only a few days. As an example, in a worst case scenario (eg. a patient with a mechanical prothesis with previous thromboemboli), the risk of a thromboembolus off warfarin could be 10 to 20% per year. Thus, if therapy were stopped for 3 days, the risk of an embolus would be 0.08 to 0.16%.
- Antithrombotic therapy should not be stopped for procedures in which bleeding is unlikely or would be inconsequential if it occurred, for example, surgery on the skin, dental cleaning, or simple treatment for dental caries. Eye surgery, particularly for cataracts or glaucoma, is usually associated with very little bleeding and thus is frequently performed without altering antithrombotic treatment.

1. Elective surgery:

a. Low risk patient:

- History of venous thromboembolism > 3 months and patients with no history of thromboembolism with aortic non-caged ball heart valves.
- Temporary discontinuation of oral anticoagulants for 7-10 days appears to be safe (ie. 4 days prior to surgery and 2-3 days postop, INR should be done a day before surgery and small dose Vit K eg. 1mg SC can be administered if required). DVT prophylaxis may be needed.

b. High-risk patient:

- First month after venous or arterial thromboembolism and in patients with caged-ball prosthetic valves, mechanical mitral valve, atrial fibrillation, left atrial thrombus, previous systemic embolization, severe left ventricular dysfunction (EF < 0.3)
- It is advisable to stop oral anticoagulants 3-4 days (longer if INR > 3.0) before surgery and start IV heparin when INR <2 to maintain PTT 2X the control level. The heparin may be infused up to 6 hours before surgery and resumed (without bolus) 12 hours after surgery (longer if any evidence of bleeding from surgical site) until oral anticoagulant therapy can be reestablished at optimal levels (usually 2-3 days post-op). SC heparin 5000-7500 U bd can be given during the intervening period.

2. For dental extractions, omission of warfarin for 1-2 days to adjust the INR to the lower limit of the therapeutic range is adequate (INR should be tested just prior to the procedure). The usual dose of warfarin can be resumed the day after surgery.

F Footnotes

Some clinically im[ortant drug interactions with warfarin

Interacting drug	Effect on warfarin
Cholestyramine Carbamazepine Griseofulvin Oral contraceptives Phenobarbitone Phenytoin Rifampicin Vitamin K	Reduced anticoagulant effect
Amiodarone Aspirin Alcohol Chloramphenicol	Increased anticoagulant effect

Cimetidine
Ciprofloxacin
Danazol
Fluconazole; ketoconazole
Mefenemic acid
Metronidazole
Omeprazole
Sulphonamides
Simvastatin
Sodium valproate
Tamoxifen
Thyroxine

_ TRANSFUSION MEDICINE

A Blood product transfusion

I. RBC transfusion

- Transfusion should generally be avoided in asymptomatic patients. Patient's age, cause and severity of anemia, and coexisting disorders such as cardiopulmonary disease must be considered when determining the need for transfusion.
- Adequate tissue oxygenation can usually be attained with a Hb of 7-8g / dl in a normovolaemic patient.
- If the cause of anaemia is easily treatable (eg. iron or folic acid deficiency), it is preferable to avoid transfusion.
- In some patients with advanced cardiovascular disease, significant pulmonary disease or cerebral vascular insufficiency, or in some elderly patients, symptoms develop at higher Hb levels.
- RBCs should not be used as volume expanders, to enhance wound healing, or to improve general 'well-being' if symptoms are not related to anaemia.

1. Indications:

a. Whole blood:

- Patients who have a symptomatic deficit in oxygen-carrying capacity and are simultaneously hypovalaemic with resultant hypontension not fully corrected by crystalloid or colloid infusion. In practice, whole blood is administered when blood loss exceeds 25-30% of blood volume.
- WB contains 3X sodium, 4X potassium, 3X ammonium and 3X acid as compared to PC; hence, WB should be given with caution in patients with heart, renal and liver failure.

b. Packed cell:

- The need to improve the delivery of oxygen to the tissues within a short time (as in symptomatic anaemia) without a need for volume expansion.

2. Dose infusion rate:
- The dose and infusion is determined by the clinical situation.
- In adults, transfusion of less than two units of red cells is bad clinical practice because it can be avoided.
- IV frusemide 20mg with each unit of blood can be given in some patients with impaired cardiac function to prevent circulatory overload.

3. Expected outcome:
- One unit of whole blood or packed cells should increase the Hct by 3%and the Hb by 1g / dl.

4. Compatibility:
- Crossmatching is performed before dispensing a specific unit of blood for a patient.
- ABO and Rh systems are specifically tested.

5. Special consideration:
- ***Leucocyte depleted red cell components*** have had most of the leucocytes and platelets removed. They are given to those patients who are already sensitised to HLA, granulocyte, and platelet antigens - for example, those who had multiple transfusions and had febrile reactions. At present, filtration is the most efficient method for removing leucocytes from RBCs.
- ***Washed red cells*** are rarely used and have the plasma proteins as well as the leucocytes and platelets removed. They are given to those who have been immunised against plasma proteins - for example, patients deficient in IgA who have developed anti-IgA antibodies.
- In ***emergency***, when there is no time to wait for crossmatching, ABO group specific red cells should be infused if the blood group is known and if the blood group is NOT known, ***O Rh D positive blood*** may be transfused (Rh D negative is very rare in Malaysia and it will not always be available for transfusion as emergency blood). At the first sign of a transfusion reaction the infusion should be stopped.

II. Platelet transfusion

1. Indications:

a. Therapeutic:
- Haemorrhage and platelet count <50,000 / ul or platelet dysfunction.

b. Prophylactic:
- Haematologic / oncologic aetiology of thrombocytopenia and platelet count <20,000 / ul.
- In ITP patient when the platelet count is less than 5,000-10,000 / ul (other therapy should be given concurrently).

- When the platelet count <50,000 / ul or less during major surgery or an invasive procedure or within 48hrs of surgery.

2. Dose and infusion rate:

- The average adult platelet concentrate dose is one unit of random-donor platelets (RDP) per 10 kg of body weight.
- They should be infused within 4 hours at a rate that depends on the patient's ability to tolerate the volume. They should not be kept in the fridge either at 4^{o}C or in the freezer.

3. Expected outcome:

- As a general rule, platelets counts should be obtained 18-24 hours postinfusion.
- The average-sized adult who receives one unit of RDP per 10kg of body weight should have a posttransfusion pletelet increment of 30,000-50,000 / ul (1 unit of of RDP should increase the platelet count 5,000-10,000 / ul).
- Patients who have smaller posttransfusion increment should have platelet counts performed 10-60 mins following the next platelet transfusion. If the 10-60 mins posttransfusion increment is less than 30,000-50,000 / ul (ie poor posttransfusion platelet recovery) and there is no evidence of splenomegaly or severe DIVC with hypotension, the possibility of refractoriness caused by alloimmunization should be entertained.
- Poor posttransfusion platelet survival (ie. adequate 10-60 mins but low 18-24 hours posttransfusion platelet count increments) is often seen in conjuction with fever, sepsis, mild DIVC and so on.

4. ABO compatibility:

- A and B antigens are expressed on the platelet surface. It is preferable to provide platelet transfusion from donors whose ABO types are compatible with the recipient.
- When ABO-compatible platelets are not available,it is acceptable to provide ABO-incompatible platelet transfusions. It this is the case, volume-reduced platelet transfusions should be considered. The post-transfusion pletelet increment is slightly lower when ABO-incompatible platelets are given.
- Rh immunoglobulin should be given to Rh negative females of childbearing age who receive platelets from Rh positive donors to prevent Rh incompatibility during subsequent pregnancy.

III. Fresh-frozen plasma (FFP) transfusion

1. Indications:

- Coagulations factor deficiency (factor II, V, VII, X, XI, XIII) and haemorrhage or anticipated invasive procedure.
- Rapid reversal of warfarin effect.
- Acute DIC.
- Treatment of TTP.
- Documented coagulopathy in setting of massive transfusion (>1 blood volume).
- Selected setting in patients with liver disease.
- Antithrombin III deficiency.

2. Doses and infusion:
- The average adult dose is determined by the clinical situation and the underlying disease process.
- It is reasonable to administer plasma at a dose of 12-15ml/kg of body weight followed by laboratory evaluation to determine responsiveness and to decide the interval between doses.
- One unit of FFP, measuring 200-300ml, will increase each clotting factor activity by 2-3 %.

3. ABO compatibility:
- The ABO type of the donor should be compatible with the recipient.

4. Special considerations:
- FFP contains the labile coagulation factors (VIII, V), all the other coagulation factors, and plasma proteins as well.
- FFP is generally not necessary if the PT and PTT are less than 1.5 times normal.
- FFP is thawed at 37^{o}C and must be transfused within 24 hours of thawing if used for coagulation factor replacement. Otherwise, loss of coagulation factors V and VIII may occur.

IV. Cryoprecipitate transfusion

1. Indications:
- Fibrinogen replacement eg in DIVC (the only transfusion products that contain fibrinogen).
- Factor VIII/vWF replacement.
- Factor XIII replacement.

2. Doses and infusion rate:
- The dose is calculated on the basis of plasma volume. A haemostatic dose of fibrinogen is supplied by pooling 10 bags of cryoprecipitate, which should result in an increment of about 75mg/dl in a 70-kg adult.

3. ABO compatibility:

- Compatibility testing is not required because the volume of plasma is small and no RBCs are present.
- Plasma compatibility is preferred but not essential.

4. Special considerations:
- Each bag of cryoprecipitate is prepared from one unit of whole blood; the volume varies from 5-20ml per bag.
- Each bag contains approximately 100units of factor VIII; von Willebrand factor; 200-250mg of fibrinogen; factor XIII; and fibronectin.
- Cryoprecipitate should be infused within 6 hours from the time it is thawed.

B. Complications of blood transfusion:

I. Classification of complications of Blood Transfusion

1. Acute Transfusion Reactions

A. Immune (antibody mediated):
- Acute haemolytic reactions.
- Pyrogenic reactions to white cells, platelets or HLA antibodies.
- Allergic reactions (to plasma proteins).

B. Non-immune:
- Circulatory overload.
- Citrate toxicity.
- Hyperkalaemia.
- Clotting abnormalities.
- Metabolic problems.
- Aggregates and pulmonary infiltrates.
- Air embolism.
- Thrombophebitis.

2. Delayed Transfusion Reactions

A. Delayed Immune:
- Alloimmunization.
- Delayed haemolytic reaction.
- Graft vs. host disease.
- Posttransfusion purpura.

B. Delayed nonimmune:
- Infection.
- Iron overload.

II. Acute Haemolytic Reactions

- Usually caused by preformed antibodies in the recipient (Ig M or Ig G classes eg. ABO antibodies) and are characterized by intravascular

haemolysis of the transfused RBCs soon after the administration of the incompatible blood.

1. Clinical Features:

- ***Haemolytic shock:*** Urticaria, pain in the lumbar region, flushing, headache, precordial pain, shortness of breath, vomiting, rigors, pyrexia and hypotension. There may be haemoglobinuria, jaundice and DIVC.
- ***Acute renal failure*** secondary to renal tubular necrosis may occur.

2. Investigations:

- Check for clerical errors in handling donor or recipient's blood specimens.
- The unit of blood and post-transfusion samples of the patient's blood should be sent to the lab for the following procedures:
  i) Repeat the grouping and cross-matching on pre- and post-transfusion samples and on the unit of blood.
  ii) Direct Coomb's test on post-transfusion sample.
  iii) Plasma for haemoglobinaemia.
  iv) Donor sample for blood culture.
- Post-transfusion sample of urine for haemoglubinuria.
- Blood for FBC, bilirubin, free haemoglobin at 6 or/and 24hrs after transfusion.

3. Management:

- Transfusion should be stopped immediately.
- Supportive treatment should be given to correct hypotension, control bleeding and prevent ATN.
- Airway management, IV crystalloid or colloid and inotropes as necessary.
- Further compatible transfusion may be required in severely affected patients.
- Urine output should be maintained at 100ml/hour or greater with the use of IV fluids and diuretics or mannitol, if necessary. The excretion of free haemoglubin may be aided by alkalinization of the urine. Sodium bicarbinate may be added to IV fluids to increase the urinary PH to 7.5 or greater.
- Broad spectrum antibiotics should be given if bacterial contamination of donor blood is suspected.

III. Pyrogenic (Febrile) Reactions

- More common in patients who have ***previously been transfused or pregnant.*** Usual cause is the presence of leucocyte or HLA antibodies in the

recipient acting against transfused leucocytes, or HLA antigens leading to release of pyrogens.

- Typical symptoms and signs are ***flushing, tachycardia, fever (>38°C), chills and rigors.***
- Treatment may include ***antipyretics, antihistamines, glucocorticoids or adrenaline*** as necessary. Acute haemolytic reaction need to be ruled out. Blood transfusion ***should be stopped.***
- Febrile reactions may be prevented by the use of leucocyte-depleted blood.

IV Allergic reactions and anaphylaxis

1. **Allergic reactions** are usually due to ***hypersensitiviy to donor plasma proteins.***

- Clinical features are ***urticaria, pyrexia, and in severe cases dyspnoea, facial oedema, and rigors.***
- Treatment is with ***antihistamines, glucocorticoids and occasionally adrenaline.*** Transfusion ***should be stopped.*** Further reactions can be prevented by giving washed red cells.

2. **Anaphylaxis** may occasionally occur especially in patients lacking IgA who produce anti-IgA that reacts with IgA in the transfused blood.

- Blood transfusion ***should be stopped*** and treatment is ***as other cause of anaphylaxis.*** If an anaphylactic reaction to blood product is suspected, the patient should have quantitation of serum IgA level before further transfusion therapy is attempted.
- Further reaction can be prevented by giving autologous blood or blood from IgA deficient donors for patients with IgA deficiency.

V Complications of massive transfusions

- Defined as replacement of a volume equavalent to the patient's normal blood volumewithin a 24-hr period.

1. **Hypothermia** due to chilled blood may cause cardiac arrhythmias. A blood-warming device can prevent this problem.

2. **Citrate intoxication** may cause hypocalcaemia and result in tetany, cardiac arrhythmias, hypotension, and decreased cardiac output. Can be treated with calcium gluconate 10% solution 10ml IV.

3. **Bleeding complications** due to dilution of platelets and coagulation factors & can be treated with FFP , cryprecipitate and platelet concentrates (4-6 units each every 10-20 units of blood transfused).

4. **Hyperkalaemia** – rare but careful monitoring for cardiac arrhythmias is required.

_ DISSEMINATED INTRAVASCULAR COAGULATION (DIVC)

- Widespread intravascular deposition of fibrin with consumption of coagulation factors and platelets occurs as a consequence of many disorders which release procoagulant material into the circulation or cause widespread endothelial damage or platelet aggregation.
- Clinical conditions associated with DIVC are:

Placental abruption
Trauma
Fat embolism
Sepsis
Promyelocytic leukaemia
Retained dead fetus syndrome
Acute intravascular haemolysis
Amniotic fluid embolus
Cardiopulmonary bypass surgery
Liver disease
Heat stroke
Burns
Vasculitis
Anoxia
Acidosis
Snake venoms
Acute pancreatitis
Near drowning

A. Clinical presentation

- It varies, with patients showing thrombotic and haemorrhagic manifestations as well as organ dysfunction in various combination. Some patients may be asymptomatic with the laboratory features of DIVC. Acute DIVC has a mortality of as high as 80%.

B. Investigation

- ***Platelet count*** is low.
- ***Fibrinogen*** titres is low.
- ***PT, aPTT, TT*** are prolonged.
- ***Factor V and VIII levels*** are low.
- ***Test for fibrin monomer complex*** (eg. ethanol gelation test or protamine sulfate paracoagulation test) are positive.
- High levels of ***fibrinogen (and fibrin) degradation products*** are found in serum and urine.
- ***PBF*** may show a microangiopathic haemolytic anaemia.

- Positive ***D-dimer test.***

C. Management

1. **Treatment of the underlying causative disorder** is most important.

2. **General supportive care:** maintenance of circulatory volume, sufficient BP & correction of hypoxaemia.

3. **Replacement therapy**:

- In patients who are bleeding or require an operation replacement of coagulation factors with fresh blood, fresh frozen plasma, cryoprecipitate and platelet concentrates is indicated.
- FFP 10-25ml/kg of body weight, cryoprecipitate 1-2 bags/10kg of body weight if fibrinogen <100mg/dl, platelets 6-8 units if platelets < 50,000 percmm and fresh blood according to Hb levels.

- Post-transfusion increments in platelet and fibrinogen levels should be checked (5,000-10,000 per ul platelet for each unit & 10 mg of fibrinogen per dl for each unit of cryoprecipitate); if such increments are not observed, repeated transfusions may be required.
- When bleeding is a problem, the approximate goal for platelet is 50,000 per ml & fibrinogen of 50-75 mg/dl.

The following therapies should be used with caution and in consultation with the physicians.

4. **Heparin**:

- The use of heparin to inhibit the coagulation process is controversial. In 95% or more of patients with DIC, the use of heparin has not been proved to be of benefit and may be harmful.
- Heparin may be used in the following situations (to be used with replacement therapy):
  - ***i) Before the induction of chemotherapy of acute promyelocytic leukaemia (less used now with the advent of ATRA).***
  - ***ii) When fibrin deposition is evident in the form of dermal necrosis (as in purpura fulminans, acral ischaemia, or venous thromboembolism).***
  - ***iii) Retained dead fetus with hypofibrinogenaemia before induction of labour.***
  - ***iv) Amniotic fluid embolism.***
  - ***v) When increases in the platelet count and coagulation factors do not occur following replacement therapy and the patient continues to bleed.***
- Low dose heparin eg. at 500U/hour or 7.5-10U/kg/hr IV infusion can be given together with fresh frozen plasma (to provide Antithrombin III).

- The heparin dose should be adjusted by monitoring the platelet count and the fibrinogen titer every 4-6 hrly. It can also be monitored with PTT determined on mixture of patient's plasma with normal 50/50 ratio (if PTT is already prolonged) and aims for 1.5X normal control.

5. Antifibrinolytic therapy:

- Individuals who have uncontrolled coagulopathy despite aggressive transfusion therapy and heparin and those with disproportionate fibrinolysis may benefit from antifibrinolytic therapy.
- Antifibrinolytic therapy should NEVER BE USED ALONE because blockage of the fibrinolytic system during ongoing DIC can produce disastrous thrombotic results. Concomitant heparin must be given.
- **EACA** (epsilon-aminocaproic acid) either 1g PO every 2 hours or as a 3-4g IV bolus followed by continuous IV infusion at 1g/hour.
- **Tranexamic acid** can be given as oral or IV 500mg-1g 3-4 times daily for 4-5 days.

8. POISONING AND DRUG OVERDOSE

_ GENERAL PRINCIPLES

1. Diagnosis

- Recognition of poisoning requires a high index of suspicion. History may be misleading or non indicative of poisoning. Drugs ingested and dosages should be sought from patient's family or friends, GP with an appropriate degree of urgency, commensurate with the clinical presentation or the assessed potential toxicity of the suspected poison, etc. Assistance from poison centres, manufacturers, etc will be needed if the actual nature of the poison is unclear from the proprietary names elicited. Recognition of specific toxic syndromes is helpful. Screening of blood, urine, or gastric aspirate for specific agents is important.

2. Supportive care

- Airway, breathing and circulation must be maintained. Endotracheal intubation may be required to protect the airway especially if gastric lavage is indicated in a drowsy patient.
- Hypotension should be treated with IV fluid; inotropes may also be needed.

3. Drug Manipulation

1. Prevention of drug absorption:

a. Emesis:

- Ipecacuanha syrup is a useful emetic in children (in doses of 10-30ml repeated once in 20 min if necessary). It is less effective and is seldom used in adults. If no response is achieved after the second ipecac dose, the patient should undergo gastric lavage.
- ***Contraindications*** to ipecac include decreased level of consciousness, absent gag reflex, caustic ingestion, petroleum products poisoning (unless the patient is intubated), convulsions or exposure to a substance likely to cause convulsions, and medical conditions that make emesis unsafe.

b. Gastric Lavage:

- Useful if performed < 4 hours of ingestion of poison except salicylates, quinidine, and tricyclic antidepressants or other agents which slow down peristalsis.
- Lavage is ***contraindicated*** in petroleum products poisoning, corrosive ingestion, convulsion and drowsy or comatose patients (unless there is a good enough cough reflex or the airway can be protected by a cuffed endotracheal tube).

- Lavage with 200ml boluses of warm saline, repeated until the effluent is clear, is followed by instillation of activated charcoal and a single dose of cathartic.

c. Charcoal:

- If administered promptly (within 4 hours) and in sufficient quantity, activated charcoal significantly reduces the GI absorption of many drugs.
- Repeated doses of activated charcoal by mouth enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with ***aspirin, carbamazepine, dapsone, digitoxin, digoxin, phenobarbitone and other barbiturates, phenytoin, quinine, tricyclics & theophylline.***
- The usual adult dose of activated charcoal is 50g initially then 25g every 4 hours.
- Activated charcoal should not be given in conjunction with an oral antidote, as it may bind and inactivate these agents.

d. Cathartic:

- The added efficacy of a cathartic is not clear, but it does decrease transit time through the intestine.
- Acceptable forms include ***magnesium citrate*** 4ml/kg (300mg maximum), ***sorbitol*** 1-2g/kg (150g maximum), and ***magnesium or sodium sulfate*** 25-30g.
- Magnesium salt should not be given in renal failure.

2. Increased Excretion:

a. Forced alkaline diuresis:

- Promotes excretion of drugs that are weak acids, eg. ***salicylates, barbital and phenobarbital.*** Forced acid diuresis is no longer recommended for any agent.
  N.B. Ensure excellent renal function. There should be at least 4 ml/min of urine output for the procedure to be safely performed.

b. Extracorporeal Techniques:

- ***Peritoneal or haemodialysis:*** Useful for ***salicylates, phenobarbitone, ethanol, methanol, ethylene glycol, and lithium.***
- ***Haemoperfusion:*** This involves the passage of heparinised blood through devices containing absorbent particles, such as activated charcoal or resins, to which drugs are adsorbed. Useful for short- and medium-acting barbiturates, choral hydrate, theophylline.

3. Specific antidotes:

- Specific antidotes are available for a small number of drugs (see individual sections).

_ DIGOXIN

- Overdosage of digoxin usually arises from its therapeutic usage.

A Symptoms and signs

1. **GI:** Diarrhoea, vomiting, abdominal pain, intestinal ulceration.

2. **CNS:** Headache, anorexia, confusion, convulsions.

3. **Visual:** Xanthopsia, haloes, blurring.

4. **Cardiac:** Arrhythmias (atrial fibrillation with slow ventricular response, non-paroxysmal AV junctional tachycardia, atrial tachycardia with varying block[SVT with block], sinus bradycardia, frequent ventricular ectopic beats, ventricular bigeminy, ventricular tachycardia), worsening of heart failure. Arrhythmias not seen with digoxin toxicity include: sinus tachycardia, RBBB, LBBB, hemiblocks and parasystole.

5. **Others:** Hyperkalaemia in acute overdose, hypokalaemia or normokalaemia in chronic overdose.

 # ECG manifestations of digoxin therapy (not overdose)

- Prolonged P-R interval.
- Shortened Q-Tc
- S-T depression(reverse-tick); T-wave flattening.

B. Predisposing factors to digoxin toxicity

- General - Old age, hypoxia, acidosis, pre-existing myocardial disease.
- Hypokalaemia, hypomagnesaemia, hypercalcaemia.
- Renal impairment.
- Hypothyroidism.

C. Management of digoxin toxicity

1. ***Cease digoxin administration***, ***gastric lavage*** and repeated doses of ***activated charcoal*** in accidental or deliberate self-poisoning.

2. ***Correct precipitating factors:***
- Aim to maintain serum potassium between 4.5 and 5.5mmol/L.
- Continuous ECG monitoring is needed.

3. ***Supraventricular tachycardia***: propanolol (Only if very fast and haemodynamically significant. Beware of the potentiating effect of beta blockage in producing a complete heart block or a severe sinus bradyarrhythmias).

4. ***A-V block:*** Atropine, isoprenaline infusion, or temporary pacing.

5. ***Ventricular arrhythmias:*** Phenytoin, lignocaine, temporary pacing.

6. ***Cardioversion*** is contraindicated and only used in life threatening arrhythmias, as last resort & used only with lower energies (10-25J)

7. ***Digoxin-specific Fab antibody fragments:***
- Indications for treatment with Fab include ventricular tachycardia or ventricular fibrillation, severe bradyarrhythmias, or a serum K concentration greater than 5mmol/l (in an acute overdose).
- Should be administered IV over 30 mins or as a bolus if cardiac arrest is imminent.
- Dosage varies based on amount of drug to be neutralized and can be estimated as followed:

Dose (No of vials) = 1.67 x amount ingested (mg) in acute over dose

or

Dose (No of vials) = digoxin level (ng/ml) x wt (kg) x 0.01 in overdose due to chronic therapy

- If toxicity results from acute digoxin ingestion and neither a serum digoxin level nor an estimate of the ingested amount is known, 10-20 vials (380-760mg) should be administered.

8. Forced diuresis, haemodialysis and haemoperfusion do not enhance the elimination of digoxin bacause of its large volume of distribution.

_ PARAQUAT

- Paraquat is found in commonly used brands of weedkiller as an aqueous 20% solution (Gramoxone) or 2.5% solution (Weedol).
- This is a very toxic agent and it is essential that treatment must be started at the earliest opportunity.

A Symptoms and Signs

- Ulcers in the mouth and oesophagus, diarrhoea, vomiting, epistaxis, pulmonary oedema, hepatocellular necrosis, acute renal failure and later pulmonary fibrosis (due to selective accumulation of paraquat in lung tissues).

B Investigations and Monitoring

- Send gastric lavage / aspirate, urine and blood for toxicology screening.
- Send gastric lavage / aspirate and urine for paraquat.
- Urine for paraquat daily for 3 days.
- BUSE daily.
- FBC, LFT, Se Creatinine and CXR once every 3 days.
- ABG.
- Strict I / O charting; assess chest and CVS for signs of fluid overload and pulmonary fibrosis regularly.

C Management

- Stomach washout as soon as possible.
- Insert nasogastric tube.
- 300ml of Fuller's earth via NG tube as soon as possible, then 20ml of Fuller's earth every hour until diarrhoea and passage of Fuller's earth.
- Magnesium sulphate (Mist alba) 30ml every 4 hours for until diarrhoea and passage of Fuller's earth or mannitol 20% 200ml as stat dose.
- 10 tabs of activated charcoal 6hrly for several days.
- IV fluids approx. 4-5 litres / day (NS and D5%) for the first 24 hours, then approx. 3 litres / day orally or IV subsequently for several days. In established renal failure, IV or oral fluids should be restricted.
- Potassium supplement either IV or orally depending on BUSE.
- Frusemide 40mg bd IV or oral for several days.
- Haemodialysis or charcoal haemoperfusion may be useful if started early.
- Oxygen is to be avoided unless PaO2 falls to <60mmHg or clinically very cyanosed (Oxygen tends to increase the toxic effects on the lungs).
- Allow liquid diet as soon as patient able to tolerate.
- Other supportive measures.

_ ORGANOPHOSPHATE & CARBAMATE

- Organophosphorus insecticides include malathion, parathion, dichlorvos, and diazinon.
- Organophosphorus insecticides irreversibly inhibit acetylcholinesterase and nicotinic synapses.
- Organophosphates can be absorbed through the skin, lungs, and GI tract.

A. Clinical manifestations

- Manifestations occur 30 min to 2 h following exposure.
- Poisoning is characterized by wide-spread muscarinic and nicotinic effects.
- ***Muscarinic effects:*** nausea, vomiting, abdominal cramps, urinary and faecal incontinence, bronchorrhoea, diaphoresis, salivation, lacrimation, cough and dyspnoea. In severe cases, bradycardia, conduction block, hypotension, and pulmonary oedema may occur.
- ***Nicotinic effects:*** Twitching, fasciculations, weakness, cramps, hypotension, and hypoventilation with respiratory failure.
- ***CNS effects:*** Anxiety, restlessness, tremor, convulsions, confusion, weakness, and coma.

B. Investigations

- Cholinesterase activity in plasma and in red blood cells is reduced to less than 50% normal.
- Insecticides may also be identified in urine on toxicology screen.
- FBC, BUSE, serum creatinine, blood sugar and ABG should also be done.

C Management

- Remove contaminated clothing, and wash skin and mucous membranes with copious amount of water.
- If drug was ingested, remove by induced vomiting or gastric lavage, followed by activated charcoal.

- Prevent hypoxia with oxygen supplement or ventilation.

1. Atropine:

- A muscarinic receptor antagonist, less effective for CNS toxicity and ineffective for nicotinic effects.
- An initial dose of 0.5-2mg given IV every 15-20 min until atropinization is adequate (manifested by flushing, dry mouth, heart rate of >120, and dilated pupils).
- The alternative is a continuous infusion (mix 8mg of atropine in 100ml of normal saline) at a rate of 0.02-0.08mg / kg / hour (0.25-1ml / kg / hr) with additional 1-5mg boluses as needed to dry the secretions.
- Patient may require 40-1500mg / day of atropine.
- The patient should be kept well-atropinized for at least 5-7 days by either intermittent administration or continuous infusion.
- Watch out for signs of over-atropinization: very dry mouth and skin, PR > 160 / min.
- Atropine should not be stopped prematurely. As the patient's poisoning state wears off, the impact of atropinisation becomes greater for a given dose of atropine. Down titration and weaning off is the preferred way to stopping treatment and would prevent rebounce pulmonary odema, etc.

2. Pralidoxime:

- An oxime that reactivates phosphorylated cholinesterase. Effects are mainly at the skeletal-neuromuscular junctions (nicotinic effects). Also has antimuscarinic and possibly CNS effects.
- Most effective when given within 24 hours of exposure to poison (Even severe poisoning may be reversed if drug is given with 48 hrs).
- The dose is 1-2g IV in 100ml of NS over 5-20 mins and repeated doses doses or, in severe cases, an IV infusion of up to 500mg / hour may be required (Max. 12g in 24 hrs).
- It should only be started after maximal atropinisation.
- It is ***contraindicated*** in certain organophosphorous poisoning eg. carbamate and to organophosphorus compounds without anticholinesterase activity.

3. Diazepam IV may help to prevent seizures and reduces twitching of muscles. Phenothiazines, morphine, pethidine, aminophylline may potentiate organophosphorus.

 # Carbamate poisoning causes signs and symptoms similar to those seen in organophosphate poisoning. Atropine administration is adequate. Pralidoxime should not be given.

_ PARACETAMOL

- Paracetamol is converted to a toxic metabolite, N-acetyl-p-benzoquinonimine, which is normally inactivated by conjugation with reduced glutathione. After a large overdose, glutathione is depleted and the toxic metabolite binds to liver cell membranes causing necrosis.
- Liver necrosis can occur with as little as 10g (20 tabs).

A. Clinical Features

- Symptoms over the first 24 hours include anorexia, vomiting, and diaphoresis, but the patient is fully conscious.
- Hepatic enzymes begin to rise 48 hours after ingestion and peak at 72-96 hours. Recovery starts after approximately 4 days unless hepatic failure develops.

B. Management

- In patients who present within 4 h of ingestion, ***gastric emptying/lavage*** should be done. Alternatively, ***activated charcoal*** can be used.
- In patients who present within 0-24 h of ingestion, ***measurement of the plasma-paracetamol concentration*** should be done at an interval of not less than 4 hours after ingestion (earlier samples may be misleading), and this is the best predictor of hepatotoxicity.
- Those whose concentrations are above toxic levels ***(refer to nomogram for paracetamol intoxication)*** are treated either with ***acetylcysteine IV*** or ***methionine by mouth***. Patients on enzyme-inducing drugs (eg. carbamazepine, phenobarbitone, phenytoin, rifampicin and alcohol) may develop toxicity at lower plasma-paracetamol concentrations: they should receive acetylcysteine if their plasma-paracetamol concentrations are 50% or more of the standard reference values.
- Treatment should be started within 8-10 hrs for maximum protective action. If a potentially toxic dose of paracetamol has been taken, treatment must be given at once and stopped if the concentration subsequently found to be below the treatment line.
- ***Acetylcysteine*** is given by IV infusion in D5%, initially 150mg/kg in 200ml over 15 min, followed by 50mg/kg in 500ml over 4 hours, then 100mg/kg in 1000ml over 16 hours. Acetylsteine should be used cautiously in asthmatic as it may cause bronchospasm. Other adverse effects are rashes and anaphylaxis.
- ***Methionine*** 2.5g orally every 4 hours for 4 doses can be given as alternative.
- AST,ALT, Bilirubin, BU, prothrombin time, and se creatinine should be done daily for 3 days. Other supportive measures should also be given as indicated.

Nomogram for paracetamol intoxication. Start antidotes therapy if levels and time coordinates are above the lower line on the nomogram. Continue and complete therapy even if subsequent values fall below the toxic zone. The nomogram is useful only in acute, single ingestions (From Rumack BH, Matthew H):

_ SALICYLATES

- Salicylate poisoning can be due to ingestion of aspirin or LMS (1ml of 25% LMS = 300mg salicylate).
- Ingestion of 10-20g of aspirin may be lethal.

A. Pathophysiology

- Salicylates stimulate the respiratory centre, producing hyperpnoea, CO2 loss, and thus causing respiratory alkalosis. To compensate, the kidneys excrete increased amounts of bicarbonate, potassium, and sodium but retain chloride leading to hypokalaemia and dehydration.
- Salicylates interfere with carbohydrate metabolism and lead to the accumulation of lactic acid, ketones, and inorganic acids producing metabolic acidosis. Hypokalaemia usually develops in mild intoxication, but hyperkalaemia occurs in severe intoxication.
- Salicylates stimulate metabolism and produce hyperthermia.
- Salicylates cause hepatocyte damage, resulting in increased plasma enzyme activity and prolongation of prothrombin time. Salicylates also decrease platelet aggregation.

B. Clinical features

- ***Mild poisoning:*** Vomiting, tachycardia, hyperpnoea, fever, deafness, tinnitus, lethargy, confusion, respiratory alkalosis, and an alkaline urine (PH >6).
- ***Severe poisoning:*** Convulsions, coma, respiratory and cardiovascular failure, dehydration, acute renal failure, and acidosis. Other complications include hypoglycaemia, cerebral and pulmonary oedema.

C. Investigations

- Salicylates are identified by a positive ferric chloride test on either blood or urine sample.

- Blood salicylates level should be taken: Level >70mg / dl at any time represents moderate to severe intoxication; levels greater than 100mg / dl are very serious and often fatal.
- An elevated haematocrit, white blood cell count, platelet count, hyponatraemia, hypernatraemia, hyperkalaemia, hypokalaemia and hypoglycaemia may be seen.
- Respiratory alkalosis coupled with metabolic acidosis, respiratory alkalosis, metabolic acidosis, and mixed respiratory and metabolic acidosis may be present.
- Prothrombin time may be prolonged.

D Management

- ***Gastric lavage*** should be performed up to 12-24 hours. Activated charcoal in repeated doses should be given.
- ***Correct dehydration and alkalosis*** with 0.9% NS and potassium as indicated. Correct electrolytes imbalance. Oxygen and glucose may be needed.
- ***Vitamin K*** IM or IV may be required to correct hypoprothrombinaemia.
- ***Treat acidosis*** with bicarbonate if severe (eg. PH <7.15).

- ***Forced Alkaline diuresis*** is indicated if ***(i) Salicylate level >50mg/dl (ii) Clinical condition is poor.***
  - # Ensure good renal function, with initial fluid replacement if volume deficit is suspected if necessary. A urine flow rate of at least 4 ml / min is necessary before forced diuresis can be safely initiated. If not, give IV frusemide 20-40mg IV. If urine output still < 4ml / min then renal insufficiency is present and abandon procedure.
  - # Regime of IV infusion:
    (i)500ml D5% with 50ml of 8.4% NaHCO3.
    (ii)500ml D5% with 1 g KCL (if no hyperkalaemia).
    (iii)500ml NS with 40mg frusemide.
    give at a rate of 500ml per hour.
  - # The above cycle can be repeated at 2 or 3 times maintenance fluid requirment for 24-48 hours; monitoring urine output (target >4ml / hr and intake = output), urine PH (target 7-8), and serum potassium.
  - # If the patient is acidotic and the serum PH is <7.15, an additional 1-2 mmol / kg of NaHCO3 should be given over 1-2 hrs.
  - # Carefully monitor for fluid overload in those at risk of pulmonary and cerebral oedema (eg. the elderly). Forced diuresis should be stopped in oliguric patients.
  - # Serum salicylate levels should be checked regularly until a consistent downward trend is noted.

- ***Haemodialysis/Haemoperfusion/Peritoneal dialysis*** is indicated in (i) severe cases, blood level>100mg / dl (ii) refractory acidosis (iii) severe CNS symtoms (iv) progressive clinical deterioration (v) pulmonary oedema (vi) and renal failure.

_ ETHANOL AND OTHER ALCOHOLS

I. Ethanol

- It is found as a solvent in some cosmetic and antiseptic preparations, as well as being a constituent of alcoholic drinks.

A. Clinical features

- Refer to table below.
- Manifestations of serious head injury may be identical or clouded by ethanol intoxication.

Blood ethanol level	Behavioral and Other manefestations
100mg / dL	Altered bahevior, impaired judgment, slurred speech, unsteady gait, labile affect, talkativeness.
200mg / dL	Profound effect on motor area of brain. Severe hypoglycaemia.
300mg / dL	Arousable unresponsiveness (stupor) with severely disturbed sensory perception.
400mg / dL	Unarousable unresponsiveness (coma), perception oblitered.
500mg / dL	Respiratory centre paralysis, metabolic acidosis and death.

B. Management

- Protect the airway, and screen for other causes of stupor or coma (if present). ***A CT scan*** of the head is indicated in any intoxicated patient who has a history of significant head injury with a GCS of <15.
- ***Gastric lavage*** if large amount has been taken within 4 hours. Charcoal is not helpful.
- ***Thiamine*** 100mg IM or IV stat then orally daily for 3 days.
- ***Glucose*** IV 50ml or 50% dextrose water to correct for alcohol-induced hypoglycaemia.
- ***Haemodialysis*** may be useful for life-threatening overdoses.
- Severely intoxicated patients may have hypoxia and PCO2 retention and may require ***intubation and ventilatory*** support. Hypotension is usually reversible with fluid replacement and rarely requires inotropes.
- Treatment of other alcohol related problems.

II. Methanol and Ethylene glycol

- Methanol (CNS depressant) is a component of shellacs, varnishes, paint removers, windshield-washer solutions, and copy machine fluid.
- Ethylene glycol is commonly used as a coolant and preservative and is found in polishes and detergents.

A. Clinical features and diagnosis of Methanol poisoning

- Methanol is metabolized to formaldehyde and formic acid, which in turn causes metabolic acidosis and injury to the retina.
- Onset is variable (12-18 hr after ingestion) and may be delayed. Early manifestations are caused by methanol, and late manifestations are due to the metabolite formic acid.

- ***Methanol*** produces ***nausea, vomiting, abdominal pain, headache, vertigo, and confusion at low overdose.*** In ***large overdose, obtundation, convulsions, and coma.***
- Late manifestations include an ***increased anion gap, metabolic acidosis***, and ***retinal injury*** (due to formic acid, lactic acid and ketones). Opthalmological manifestations (occur 15-19 h later) include ***clouding and diminished vision, dancing and flashing spots, dilated or fixed pupils, hyperaemia of the disc, retinal oedema, and blindness.***
- Early diagnosis is suggested by ethanol-like signs of intoxication and an elevated serum osmolality and is confirmed by measurement of serum methanol (usually > 20mg / dL) 12-48 hrs following ingestion.
- The diagnosis of methanol-derived formic acidosis is suggested by a large anion gap, a low serum bicarbonate, an elevated serum formate level, and an elevated blood methanol.

B. Clinical features of Ethylene Glycol poisoning

- Ethylene glycol poisoning often exhibits three distinct clinical phases after ingestion due to the toxic metabolites glycolate, glyoxalate and oxalate.
- First, ***within 12 h, CNS effects*** predominate. The patient appears intoxicated without the odor of ethanol in the breath.
- Second, ***12-24h*** after ingestion, ***cardiopulmonary effects*** predominate. Elevated heart and respiratory rate and blood pressure are common. CHF, ARDS, and circulatory collapse are also noted.
- Third, ***24-72h*** after ingestion, ***renal effects*** predominate. Acute tubular necrosis with acute renal failure occurs if appropriate treatment is not received.
- Hypocalcaemia may result from precipitation of calcium oxalate into tissues and may be severe enough to cause tetany and typical ECG changes. Calcium oxalate crystals are noted on urinalysis. Elevated CPK may be seen and leukocytosis is common.
- High anion gap metabolic acidosis and a high osmolal gap (Osm measured - Osm calculated [normal <10 mosm / L]) may be found.

C Management

- Treatment of methanol and ethylene glycol poisoning are similar.
- ***Gastric lavage*** if < 4 hrs of ingestion.
- If seizures occur, exclude hypocalcaemia and treat with iv ***diazepam.*** If hypocalcaemic seizures occur, treat with 10 to 20 ml of 10% ***calcium gluconate.***
- Correct acidosis with ***sodium bicarbonate*** (Methanol is metabolised slowly and the patient may relapse if bicarbonate administration is discontinued too soon).
- Inhibit metabolism with ***ethanol:*** alcohol dehydrogenase (which oxidises methanol to formaldehyde and then to formic acid; also metabolizes ethylene glycol) has a much higher affinity for ethanol and hence ethanol is

used to competitively inhibit the metabolism of methanol and ethylene glycol.

- Ethanol therapy is indicated in (***i) suspected methanol or ethylene glycol poisoning (ii) patients who have a methanol or ethylene glycol level > 20-30mg/dL (iii) the presence of an anion gap metabolic acidosis with an osmolal gap.***
- A single dose of ethanol (IV or Oral) 0.5-1.0g / kg BW is followed by maintenance dose which varies depending on previous alcohol exposure (average 80-120mg / kg / hr). The goal is to achieve blood alcohol level of 100-200mg / dL until methanol or ethylene glycol level falls below detectable level and all signs of toxicity are resolved.
- If necessary, oral therapy with commercial alcoholic beverages can be initiated (eg. 125ml of gin, whisky or vodka) followed by further oral doses or by IV infusion.
- For patients seen late (12-24h) after ingestion, ethanol should be used to block further conversion of methanol to formic acid.
- ***Haemodialysis*** is indicated when ***methanol or ethylene glycol levels are >50mg/dL, patients with visual signs, and when clinical or metabolic abnormalities are unresponsive to the preceding therapy.*** Haemodialysis is two to three times more efficient than peritoneal dialysis. If dialysis is employed, increased quantities of ethanol must be administered, as ethanol is readily dialysable.
- ***Folinic acid,*** 30mg iv 6hourly, may protect against ocular toxicity by accelerating formate metabolism in methanol poisoning. ***Thiamine*** and ***pyridoxine*** (100mg IV or IM q day), are administered to drive the metabolism of ethylene glycol to non-toxic metabolites.

_ OPIOIDS

- Example of opioids are heroin, morphine, methadone, meperidine, pethidine, propoxyphene, hydromorphone, oxycodone, pentazocine, codeine, etc.

A. Symptoms and Signs of Opioids overdose

- The triad of ***coma, pin-point pupils, and depressed respiration*** (may be as low as 2-4/min) strongly suggests opioid overdose. Less common complications include hypotension, bradycardia, hypothermia, convulsion, cardiac arrhythmias, renal failure and pulmonary oedema. Pupils may be dilated with acidosis or hypoxia.

B. Management

- Maintain the ***airway*** and assist ventilation if necessary.
- Give ***Oxygen***.
- Treat coma, seizures, hypotension, and noncardiogenic pulmonary oedema if they occur.
- ***Naloxone***, a pure opioid antagonist, is used in all cases of suspected opioid overdose. It is also useful when opioids are used together with alcohol or central nervous system depressants.

- IV naloxone, 0.4-1.2mg repeated at intervals of 3-5mins to achieve a respiratory rate of about 15/min or max. of 10mg if respiratory function does not improve (then question diagnosis). Subcutaneous or intramuscular injection can be given if IV access is not available (onset of action slower).
- Naloxone's duration of action is shorter than that of most opioids, therefore, repeated injections are necessary according to the respiratory rate and depth of coma. Alternately, it may be given by continuous IV infusion (eg. 2mg diluted in 500ml of 5% dextrose or NS starting at a rate of 100ml/h and adjusted according to response).
- Watch-out for ***signs of over-treatment; hyperventilation, muscle tremor, tachycardia and hypertension.***
- Acute withdrawal symptoms ***(abdominal pain, sweating, dilated pupils, diarrhoea, tremors and pilo-erection)*** may develop in chronic narcotic abusers and careful titration of the naloxone doses may prevent this.
- If the opioid has been taken orally, ***gastric emptying*** may be of value for up to 12 hrs because of opioid-induced delay in gastric emptying.
- ***Intermittent Positive Pressure Ventilation*** may be required in pulmonary oedema (diuretics should not be used since it is due to leakage from pulmonary capillaries and not to fluid overload).

_ ACIDS AND ALKALI

- ***Common acid products:*** toilet bowl cleaners (hydrofluoric, phosphoric, sulfuric acids), soldering fluxes (hydrochloric acid), antirust compounds (hydrofluoric, oxalic acids), automobile battery fluid (sulfuric acid), and slate cleaners (hydrofluoric acid).
- ***Common alkaline products:*** industrial-strength bleach, drain cleaners (sodium hydroxide), surface cleaners (ammonia, phosphates), laundry and dishwasher detergents (phosphates, carbonates), disc batteries, denture cleaners and clinitest tablets.

A. Clinical Features:

- **Alkali** produce liquefactive necrosis with rapidly penetrating tissue burns and higher risk of perforation of the oesophagus than do acids. **Acids** produce coagulative necrosis. Both burn the mouth, oesophagus, and stomach.
- **Clinical:**
  1. ***Burns of the mouth***: excessive salivation, pain, dysphonia and dysphagia. Erythema, oedema, ulceration, and necrosis may be seen.
  2. ***Oesophageal injury:*** drooling, painful swallowing, vomiting of blood and mucus, retrosternal pain, and neck tenderness. Perforation may be suggested by increased severity of chest pain, respiratory distress.
  3. ***Stomach burns:*** Epigastric pain, vomiting, and tenderness.
  4. ***Aspiration:*** fulminant tracheitis and bronchopneumonia.
  5. ***Severe cases:*** Hypotension, shock, metabolic acidosis, liver and renal dysfunction, haemolysis, and DIVC.
  6. ***Late complications:*** oesophageal stricture and gastric outlet obstruction.

B. Management

- ***Immediate rinsing*** of oral cavity with copious cold water.
- ***Induction of emesis, lavage, or charcoal administration is contraindicated.*** Attempting to neutralize the agent with a weak acid or base will result in an exothermic reaction and increase tissue damage.
- ***Airway*** should be protected, oxygen administered, and fluids given as appropriate. Intubation and ventilation may be required.
- Prevention of of oesophageal stricture with ***glucocorticoid is controversial.*** Prednisolone 1-2mg/kg/day tapered over 3 weeks can be given if used.
- Prophylactic antibiotics are controversial.
- ***Endoscopy*** should be safe within 48 h (optimally 12-24h) of the ingestion and should be done in all symptomatic patients. Surgical consultation should be obtained.
- Grading system for corrosive burns of the alimentary tract:

Grade	Features
1	Erythema and oedema only
2a	Localized, superficial friability, blisters or ulceration
2b	Features as for grade 2a but with circumferential ulceration
3	Multiple deep ulcers, areas of necrosis

- Patients with ***first degree oesophageal burns*** may be discharged if they are able to take fluids orally.
- Patients with ***second-degree burns*** should be admitted to a general ward and given parenteral nutrition during the initial catabolic phase. Oral fluids can normally be given by day 7, and solids as tolerated thereafter.

- Patients with ***third-degree burns*** should be managed in ICU. TPN or a feeding jejunostomy will be required until the gastrointestinal lesions have healed.
- ***Laparotomy*** with resection of necrotic tissue and surgical repair is recommended when:
  i) Endoscopy reveals evidence of Grade 3 burns with full thickness necrosis (blackened, ulcerated mucosa) of the stomach or oesophagus.
  ii) Symptoms or signs of gastrointestinal perforation are evident at the time of initial presentation.
- Late complications can be assessed by barium swallow (at 2-4 weeks).

_ BENZODIAZEPINES

- Benzodiazepine poisoning is common but death is rare, unless other potentiating agents (eg. alcohol) have also been taken.
- Benzodiazepines potentiate the inhibitory effect of GABA on the CNS.
- Examples of Benzodiazepines:
  (i) Long-acting: diazepam, chlordiazepoxide, clonazepam, flurazepam, clorazepate.
  (ii) Short-acting: alprazolam, lorazepam and oxazepam.
  (iii) Ultra-short acting: midazolam, temazepam, and triazolam.

A. Clinical Features

- Weakness, ataxia, dysarthria, nystagmus, drowsiness, confusion, coma , constricted pupil, and respiratory depression. Paradoxical excitation may occur initially.
- Confirmation of the diagnosis is made by obtaining serum levels but are rarely of value in emergency management.

B. Management

- ***Gastric lavage*** if seen early followed by single or repeated doses of activated charcoal.
- ***Supportive measures*** as in other poisonings.
- ***Flumazenil***, a competitive benzodiazepine receptor antagonist, can reverse CNS and respiratory depression and obviate the need for endotracheal intubation.
- It may be given as 200ug IV over 15s; if needed, further doses of 100ug can be given at 1 min intervals up to a total dose of 1-2 mg (Failure to respond to flumazenil suggests that benzodiazepines are not the cause of poisoning).
- Recurrence of sedation and / or respiratory depression (flumazenil has a relatively short duration of action) may be treated by repeating the above regimen or by continuous infusion of 0.1-0.5mg / hour, adjusted according to level of arousal.

_ BARBITURATES

- Barbiturates are GABA receptor agonists and inhibit excitable cells of the CNS and other tissues.
- Short-acting agents (amobarbital, secobarbital, and pentobarbital) generally cause toxicity with lower doses than the long-acting agents (phenobarbital, barbital, primidone and mephobarbital), but fatalities are more common with the latter.

A Clinical Features

- Barbiturates cause CNS depression ranging from confusion and lethargy to coma (resemble alcohol intoxication). Hypothermia, hypotension, pulmonary oedema, cardiac arrest and loss of reflexes (except pupillary light reflex) may also ocur. Bullous skin lesions may be seen in severe overdose.
- Plasma concentrations tend to correlate poorly with the severity of overdose. Signs of toxicity usually appear when serum concentrations of long-acting barbiturates exceed 4mg / dl and short-acting barbiturates exceed 2mg / dl.

B. Management

- ***Gastric lavage*** if < 4 hrs of ingestion. Multidose activated charcoal (50g 4-6hrly) markedly decreases the half-life of phenobarbital and other long-acting barbiturates.
- Maintenance of airway and adequate ventilation and tissue perfusion.
- An IV fluid challenge with crystalloid solutions is the first treatment for hypotension. Low doses of inotropic agents may be required if the pressure does not respond to fluid resuscitation.
- ***Forced alkaline diuresis,*** similar to that used for salicylate intoxication, is effective for long-acting agents but not effective for short & intermediate acting barbiturates.
- ***Haemodialysis and haemoperfusion*** are effective in removing both long- and short-acting barbiturates, and are reserved for severely intoxicated patients with high blood levels.

_ TRICYCLIC ANTIDEPRESSANTS AND RELATED DRUGS

- Tricyclic antidepressants include amitriptyline, imipramine, desipramine, nortriptyline, doxepin and protriptyline.
- Pharmacologic actions include central and peripheral anticholinergic activities, depression of myocardial contractility, slowing of intraventricular and atrioventricular conduction, and CNS effects similar to phenothiazines.

A Clinical features

- ***Anticholinergic manifestations:*** mydriasis, ileus, urinary retention and hyperpyrexia.
- ***Cardiovascular toxicity:*** supraventricular and ventricular arrhythmias, conduction blocks, sinus tachycardia, hypotension, hypoperfusion, and pulmonary oedema.
- ***CNS manifestations:*** agitation, confusion, stupor, coma, seizures.
- Metabolic acidosis.

B. Management

- ***Gastric lavage*** should be performed regardless of time of presentation, as gastric emptying is delayed by the drug.
- Repeated administration of ***activated charcoal*** is useful.
- ***Cathartic*** should be given until diarrhoea occurs.
- Forced diuresis and haemodialysis are not indicated.
- Acid-base balance should be monitored and acidosis, which increases the risk of cardiac arrhythmias, should be corrected.
- Continuous ***cardiac monitoring*** is mandatory.
- ***Alkalinization*** with IV sodium bicarbonate 1-2meq/kg, to maintain an arterial PH of 7.45-7.55, is effective in preventing and treating hypotension, arrhythmias (including SV and V arrhythmias) and conduction disturbances.
- For the intubated patient, hyperventilation to a pCO2 no lower than 25 mmHg and arterial PH of 7.45-7.55 is an effective mean of alkalinzation and avoids the administration of large amounts of sodium.
- ***Arrhythmias*** should be managed conservatively with sodium bicarbonate; this treatment may successfully abolish arrhythmias even in patients without acidosis.
- Unless cardiac output is significantly compromised, anti-arrhythmic drugs are not used because they have negative inotropic and membrane effects, which may aggravate the adverse effects of tricyclics on the myocardium. Lignocaine and phenytoin can be used if necessary. Class Ia antiarrhythmics are contraindicated.
- Temporary ventricular pacing is used for complete heart block.
- ***Hypotension*** not responsive to alkalinization and fluid administration should be treated with noradrenaline.
- ***Convulsion*** should be treated with iv diazepam and phenytoin.
- Anticholinesterases (eg. physostigmine) are no longer advocated in tricyclic poisoning, because their effects are short-lived and they may produce convulsions, confusional states and hypotension.
- Respiratory depression is common and is treated with mechanical ventilation.

_ PHENOTHIAZINES AND OTHER NEUROLEPTICS

- Examples are chlorpromazine, thioridazine, prochlorperazine, haloperidol.

A. Clinical features

- Depression of consciousness
- Hypotension
- Respiratory depression
- Miotic pupil with depressed deep tendon reflexes
- Hypothermia
- Cardiac arrhythmias (including torsades de pointes)
- Convulsion
- Extrapyramidal reactions - rigidity, bradykinesia, tremor, oculogyric crisis and dystonia.
- Anticholinergic manifestations - dry mouth, absence of sweating, tachycardia & urinary retention.

B. Management:

- Airway protection, respiratory and haemodynamic support and gastric lavage followed by administration of activated charcoal.
- Patients with significant overdosage require cardiac monitoring for at least 24-48 hours.
- ***Acute dystonic reactions***, respond to iv diazepam or to an anticholinergic agent (eg. benztropine).
- Specific drug therapy is usually not indicated for parkinsonian features which will often improve on withdrawal of the offending agent.
- ***Ventricular arrhythmias*** are treated with lignocaine and phenytoin; class Ia agents are contraindicated.
- ***Hypotension*** is treated by fluid administration and alpha-adrenergic vasopressors.
- Recurrent ***torsades de pointes*** may require magnesium, isoprenaline or overdrive pacing.
- ***Seizures*** are treated with diazepam and phenytoin.
- Haemodialysis and other elimination technique are not useful as most of these drugs are very lipid soluble and have high volumes of distribution.

_ THEOPHYLLINE

- Theophylline causes the release of endogenous catecholamines and prolongs their effects by inhibiting the degradation of cyclic AMP by phosphodiesterase.
- Aminophylline is 80% theophylline.

A. Clinical Features

- Nausea, vomiting, restlessness, irritability, agitation, tachypnoea, tachycardia, and muscle tremors. In ***severe overdose,*** coma, hypotension, respiratory depression, generalized tonic-clonic and focal convulsions and rhabdomyolysis may occur.
- ***Cardiovascular effects*** include atrial arrhythmias, multifocal ventricular ectopics, idioventricular rhythms, ventricular tachycardia, and ventricular fibrillation.
- ***Metabolic abnormalities*** include ketosis, metabolic acidosis, increased serum amylase, hyperglycaemia, and decreased serum potassium, and calcium.
- Toxicity occurs at lower theophylline levels with chronic than with acute poisoning.
- ***Serial serum levels*** should be measured to determine the peak concentration (therapeutic serum level are 55-110 umol/L [10-20mg/L or mcg/ml]).

B. Management

- ***Gastric lavage*** (if within 1-2 hours of ingestion) and ***multiple doses of activated charcoal***. Activated charcoal given in multiple doses will increase the elimination of theophylline from the gut.
- ***Extreme tachycardia*** is treated with propranolol or esmolol. The possibility of exacerbating pre-existing obstructive airways disease often precludes the use of such drugs.
- ***Hypotension*** is treated with volume expansion.

- ***Serum K level*** should be measured and monitored regularly. Potassium supplements are nearly always needed.
- Benzodiazepines and barbiturates are useful for convulsions and hyperactivity (Phenytoin is ineffective).
- ***Upper GI haemorrhage*** may follow theophylline-induced peptic ulceration and H2-antagonist other than cimetidine should be given since cimetidine inhibits the metabolism of theophylline.
- ***Ventricular tachyarrhythmias*** should be treated with propranolol and standard antiarrhythmics.
- ***Haemodialysis, peritoneal dialysis and haemoperfusion*** are effective in removing theophylline and are indicated ***in patients with severe toxicity or after acute ingestion with serum level > 440 umol/L [80mg/L], and in chronic ingestion, with serum levels >200-300umol/L [40-60mg/L].***

9. MISCELLANEOUS

_ SNAKE BITE

- Venomous snakes are predators. Man is not the usual prey, and consequently most instances of venomous bites in human are "defensive" bites and the amount of venom "injected" are relatively small. This is one of the factors which explain the relatively low mortality due to snake bites.
- In bites by land snakes, a general clinical yardstick is the degree and extent of tissue damage following the bites. That is, the greater the local tissue damage, the larger the amount of venom introduced and vice versa.
- In bites by sea snakes, this rule *does not* apply. The local tissue injury tends to be negligible and is often missed or ignored; the systemic and neurological impact of the venom on the other hand could be devastating.

A. Classes and features of poisonous snakes in Malaysia

1. **Elapidae:**
   Cobra-Large snake, 6'-18' long (adult), brown black in colour, erect forebody with spectacular outspread hood, hissing, no Loreal pit, third upper labial scale enlarged.
   Coral snakes-small & slender snakes, brightly coloured, no Loreal pit, third upper labial scale enlarged.
   Kraits-Body is triangular in cross section, vertebral scales enlarged, no Loreal pit, third upper labial scale not enlarged.
2. **Viperidae:**
   Vipers-Loreal pit present on head between eye and nostril, head triangular in shape, distinct neck.
3. **Hydrophidae:**
   Sea snake-Tail laterally flattened.

B. Clinically features

1. **Elapids (Neurotoxic):**

- ***Local effects***-

Type of snake	***Pain at bitesite***	Local oedema	***Pain in regional lymph nodes***	***Local necrosis***	***Local skin dicoloration***
Cobra	+++	+++	+++	+++	+++
Kraits	+	-	+	-	-
Coral Snake	+++	++	+	-	+

- ***Vomiting***- early sign of systemic envenoming.
- ***Neurotoxicity***- most important effect of elapid venoms. May appear as soon as 15-20 mins or delay for many hours. Symptoms include blurred vision,

paraesthesia around the mouth and gums, hypersalivation and drowsiness. Objective signs include ptosis, paralysis of upward gaze, total external ophthalmoplegia, inability to open the mouth, protrude the tongue, speak and swallow, respiratory paralysis and generalized flaccid paralysis.

2. Vipers (Haemotoxic):

- ***Local effects***- Pain, local swelling and bruising usually within 1-2 hours, may spread to involve the whole limb and adjacent trunk over the next 2-3 days and may cause necrosis. Tender Lymph node is common.
- ***Haemostatic abnormalities***- spontaneous systemic bleeding eg. at gingival sulci, nose, GI tract, skin and intracranial. Defibrination, causing incoagulable blood may be found.
- ***Shock***- most commonly caused by hypovolaemia, results from leakage of blood and plasma into the bitten limb or increase in capillary permeability resulting in pulmonary oedema, effusions, etc.
- ***Cardiac arrhythmias*** and ***ECG abnormalities*** may be seen; a***cute renal failure may also occur.***

3. Sea snakes (Myotoxic and neurotoxic):

- All sea snakes in Malaysia are poisonous.
- ***Local effects***- usually little pain and no oedema at the site of bite (cf. fish stings are painful).
- ***Myopathic/myotoxic effects***- generalised muscle pain, weakness and myoglobinuria. Tendon reflexes may be depressed and respiratory failure may occur.
- ***Neurotoxic*** - ptosis, trismus, blurring of vision, etc.
- ***Acute renal failure and cardiac arrest*** due to ***hyperkalaemia.***

C. Treatment of poisonous snake bites

- ***In all cases of suspected venomous snake bite, it is imperative to "diagnose" the class of snake involved, in order to predict the type of damages to be expected, and to decide on the type of anti-venom to use.***
- ***The following points could help to establish this:***
  - ***a. Make the patient describe the snake (show pictures or photographs if available).***
  - ***b. Establish the geographic location of the bite to differentiate between sea snake and land snake bites (Remember that riverine areas close to the sea might have sea snakes provided the river water is still salty).***

1. First aid:

- Reassurance- two out of 3 victims are injected with very little or no venom.
- Immobilization of the bitten limb with a splint or sling.
- Identify the snake if the snake has been killed- this is very important if the doctors are to give the right anti-venom.

- Inspect the bite: The bite of venomous land snake usually produce two clean puncture wounds (fang marks) with swelling and discolouration if significant venom has been injected. Non-venomous land snake bite produce semi-circular rows of puncture. Venomous sea snake bite also produce very negligible local effect.
- Do not cut or squeeze the bite wound.
- Rapid transport to hospital, with the bitten limb immobilised.
- Use of tourniquet is controversial. Only apply a firm but not tight tourniquiet above the bite wound with a piece of cloth, a handkerchief or other material. Ensure some circulation distally.

2. Hospital Management:

General measures:

- Look out for the symptoms and signs corresponding to the different types of venomous snakes.
- Monitor the following parameters regularly (if type of snake is unidentified):
  Local tissue inflammation, degree and extent. ***Ptosis, speech, tongue protrusion, breathing pattern, petechiae, bleeding from venepuncture site, haemoptysis, gum bleeding, muscle pain, muscle weakness, colour of urine (for haemoglobinuria), urine output and vital signs.***
- Send FBC, urine for haemoglobinuria or myoglobinuria, platelet count, group and cross match. Monitor BT, CT, PT, se K and ECG.
- Observe for at least 24 hours even if no sign or feature of venomous snake bites detectable clinically.

Treatment of specific snake bite:

a. Hydrophidae:

- When systemic poisoning occurs (symptoms and signs of neuro and myotoxicity), give 2 – 4 ampoules of sea snake antivenom IV with the earliest sign of systemic poisoning.
- Apart from antivenom, treatment of hyperkalaemia, renal failure (from myoglobulinuria) and respiratory failure (respiratory muscle paralysis) have to be instituted ie judicious use of IV fluid, diuretics, bicarbonate, insulin and dextrose to correct the electrolytes and to maintain a good urine flow to avoid renal shut down. Dialysis may be required for hyperkalaemia or renal failure and mechanical ventilation for respiratory failure.

b. Elapidae:

- If the snake is identified then specific antivenom is given. 2-10 ampoules of antivenom is required depending on severity and NOT body weight.
- Pain relief, and care of the bite area with its tissue damage must be meticulously addressed. Other supportive measures would include mechanical ventilation for respiratory failure.

c. Viperidae:

- If there is only a slight prolongation of clotting time without significant local bleeding or spontaneous systemic haemorrhage, no antivenom is

required but the patient is kept in the ward until clotting time is normal or near to normal. Fresh blood, or fresh frozen plasma as well as other blood products may be necessary to correct bleeding tendency.

- Where there is evidence of significant systemic haemorrhage, also give 2-5 ampoules of antivenom.

_ **Antivenom:**

Indications for antivenom treatment:

- **Systemic envenoming:**
  - Hypotension, shock, signs of CVS toxicity
  - Ptosis, ophthalmoplegia, respiratory paralysis
  - Impaired consciousness
  - Spontaneous systemic bleeding, non-clotting blood
  - Dark urine (myoglobinuria or haemoglobinuria)
  - Tender stiff muscles
  - Acidosis
- **Local envenoming:**
  - Swelling involving >half of the bitten limb
  - Rapid progression of swelling

a. Choice of Anti-venom and dosage:

- If the biting species is known, an appropriate mono-specific or polyspecific antivenom should be given; if the species is unknown, a polyvalent antivenom should be given.
- The initial dose of antivenom varies with the manufacturer and species of snake but is generally about 2-10 ampoules and can be repeated if no distinct clinical improvement noted within 1-2 hours (Check drug information data provided for proper dosage).

b. Method of giving anti-venom:

- Test patient's sensivity to antivenom by giving 0.2 ml subcutaneously first, observe for 30 mins.
- If no adverse reaction occurs, administer the required amount of antivenom diluted in 200ml of saline or 5%dextrose water by slow IV drip over about 1 hour.
- Adrenaline 0.5ml of 1 in 1000 should be drawn up for treatment of anaphylaxis.
- Reaction may develop despite negative sensitivity test but can be controlled by adrenaline subcutaneously with or without antihistamine and steroid.
- Routine anti-histamines SC adrenaline and hydrocortisone may be given prior to infusion to prevent reaction to antivenom.
- For a patient with a known allergic history, two iv drips should be set up; one containing antivenom, hydrocortisone and antihistamine, and the other containing adrenaline. If there is reaction, the adrenaline can be given immediately.
- A patient with positive skin reaction should be sensitized by injecting diluted serum starting with a small dose and gradually increasing the doses

at intervals of 15 mins until the total amount of serum is given. They should also be covered with adrenaline, antihistamine and hydrocortisone.

- When symptoms of snake-bite are severe it may not be advisable to wait for 30 mins to observe reactions to test-dose serum. In such cases it may be better to inject 1 ml of 1:1000 adrenaline IM at the same time as the serum in order to lessen the risk of anaphylaxis. Adrenaline may be repeated if necessary.
- For children, it is recommended that half to two-thirds of a dose should be given.
- If there is no improvement after the first dose of antivenom, a repeat treatment may be given an hour later.
- Antivenom is probably of less value after 12 h; however, it can be effective, particularly for clotting defects, even after 24 h.

Other measures:

- Antitetanus therapy should always be given and a broad-spectrum antimicrobial administered in serious cases (Where coagulopathy is evident, avoid intramuscular injections).
- Signs of hypovolaemic shock, often with concomitant lysis of RBCs and platelet destruction, require fluid and blood component replacement.
- Defect of haemostasis require replacement with specific clotting factors, fresh frozen plasma or platelets.
- Surgical debridement of blebs, bloody vesicles, or superficial necrosis, if present, should be carried out between 3rd and 10th day.

ELECTRICAL INJURIES

- Injury caused by an electric current passing through the body. The electricity may be atmospheric (lighting) or man-made; ie high-voltage transmission and low-voltage lines.

A. Pathophysiology

Electrocution

Risk of electrocution and electrical burns depend on the following:

1. Type of current - In general, direct current (DC), is less dangerous than alternating current (AC).
2. The quantity of the current (amperage).
3. The potential of the current (voltage) - Generally, the higher the voltage and the amperage, the greater the damage from either type of current.
4. The resistance offered by the body - Listed in the order of increasing magnitude of resistance are nerves, blood vessels, muscle, skin, tendon, fat, and bone.
5. The pathway of the current.
6. Duration of contact.
7. Grounding.

Lightning Injury

There are four mechanisms of lightning strike:

1. ***Direct strike*** - major current flow directly through the victim and is facilitated by metal objects.
2. ***Flashover*** - The lightning travels on the outside of the body and is facilitated by wet garments and sweat.
3. ***Side flash*** - occurs when the current splashes from a building, tree or other person and then travels to the victim.
4. ***Strike potential*** - occurs when the lightning strikes the ground close to a victim with one foot touching the ground closer to the point of the lightning strike. The lightning current may enter one leg and pass up through the victim's body and exit through the other leg.

B. Clinical features

1. **Tissue heat injury (burns)** - electric injury produces an entrance and an exit wounds. These depend on the area of contact and skin resistance. Lightning injuries are usually superficial and rarely leave entry or exit wounds. Other electrical heat generated tissue injuries include coagulation ischaemia and necrosis, and vascular thrombosis. Myoglobinuria may

results from extensive muscle necrosis and may subsequently cause acute renal failure.

2. **Cardiorespiratory system injuries** - may include asystole, ventricular fibrillation, myocardial infarction and other arrhythmias.

3. **Neurological Injuries** - these injuries may involve the central nervous system, spinal cord, and peripheral nerves and clinical manifestations may range from confusion, agitation, paresis, paralysis, autonomic nervous system dysfunction, seizures to coma and may be temporary or permanent. Neurological deficits can be seen up to 3 years after the initial injury.

4. **Musculoskeletal system** - dislocations, fractures, and blunt injuries may be present from powerful muscle contractions or falls secondary to the electric shock.

5. **Eyes and Ears** - cataracts, optic nerve damage, retinal separation and perforation, uveitis have been reported. Tympanic membrane rupture may also occur.

C. Investigation

- FBC, BUSE, creatinine, urine FEME for myoglobin, ECG monitoring, cardiac enzyme, appropriate x-rays and CT scan if indicated.

D. Management

1. First aid and resuscitation:

- At the scene of the accident, the patient must be separated immediately from the electric current, but rescuers must not touch or approach the patient until the current has been shut off or proper protective clothing is worn. Cardiopulmonary support must be initiated if necessary and maintained during transport.

2. Fluid and electrolyte:

- ***Fluid replacement*** may need to be vigorous especially in patients with hypovolaemia (normal saline or ringer's lactate) with CVP and urine output monitoring. However, in patients with suspected cerebral oedema, a judicious fluid balance should be in place.
- The presence of urinary haemoglobin and myoglobin may necessitate good hydration, and the use of mannitol or frusemide to prevent acute renal failure. The rate and volume of crystalloid infused must be sufficient to maintain a minimum urine output of 100ml/h. This infusion is continued until the urine is grossly clear of pigment.

3. Cardiac:

- ***Cardiac monitoring*** is essential and should be employed for the first 24 hrs. Cardiac arrhythmias are treated in the usual manner. Cardiac arrest and cardiopulmonary resuscitation are discussed in other sections.

4. **Treatment of burns, ischaemic and necrotic tissues**:
- The principles of management of burnt area is early excision. Fasciotomies and amputations may be necessary. Tetanus toxoid and antibiotics are given if indicated.

5. **Fractures and dislocations** are treated appropriately.

6. In patient who is unconscious and unresponsive, fluid restriction is the rule, and computed tomography is indicated to exclude a surgically correctable lesion.

_ NEAR-DROWNING

- Near drowning is defined as survival, at least temporary, following asphyxia while immersed in a liquid medium.

A. Clinical Features

1. **Lung injury:** Both fresh or salt water produce changes which lead to widespread atelectasis, pulmonary oedema, severe intrapulmonary shunting, gross ventilation-perfusion mismatch, increased pulmonary vasoconstriction, decreased compliance, and marked hypoxaemia. ARDS may follow any time up to 72 hours after the event (secondary drowning).
2. **Fluid and electrolytes changes**:
- ***Fresh water:*** Hyperkalaemia (haemolysis), hyponatraemia, hypocalcaemia, hypomagnesaemia, haemolysis with haemoglobinuria.
- ***Salt water:*** Hyperkalaemia, hypernatraemia, hypercalcaemia.
3. **CNS**:
- Cerebral oedema occurs in response to cerebral hypoxia and acidosis.

4. Miscellaneous:

- Renal failure may occur following haemoglobinuria, myoglobinuria, hypoperfusion, acidosis, and hypoxia.
- DIVC may occur.
- Hypothermia may occur.

B. Investigations

- FBC, BUSE, ABG, urine and plasma for Haemoglobin, DIVC screening, CXR, CT scan in comatose patient, ECG, etc.

C. Management

- The management of fresh water or salt water drowning is identical.

1. Oxygenation and Ventilation:

- Oxygen can be given by face mask or nasally. Intubation and mechanically ventilation should be instituted if necessary, in which event, the ventilatory mode preferred would be IPPV with PEEP.
- Bronchospasm, if present, is relieved by aminophylline and beta-2 agonists.
- Pulmonary oedema is treated using IV frusemide.

2. Circulation:

- Hypotension should be treated with fluid replacement or inotropic agents depending on vascular volume status. CVP line may be indicated.
- Packed cells may be needed when there is severe haemolysis .

3. Acidosis and hypothermia should be treated if severe.

4. Cerebral protection:

- Intracranial hypertension should be treated with hyperventilation, fluid restriction, and if renal function permits, using mannitol or frusemide. The use of steroid is controversial.

5. Antibiotic is indicated if infection is likely.

6. Others:

- Nasogastric tube should be inserted to decompress the stomach.
- Anti-tetanus toxiod.

_ ANAPHYLAXIS

- Anaphylaxis is the symptom complex accompanying the acute reaction to a foreign substance to which a patient has been previously sensitized (Type I hypersensitivity).

- Anaphylactoid reaction is used to describe reactions clinically indiscernible from anaphylaxis, in which the mechanism is non-immunological or has not been determined.

A. Causes

- Injection of drugs, blood products, plasma substitutes or contrast media, ingestion of foods or food additives, or insect stings.

B. Clinical Manifestations

1. ***Skin***- erythematous blush, generalized urticaria, angio-oedema, conjunctival injection, pallor.
2. ***CVS***- tachycardia, arrhythmias, hypotension, and shock.
3. ***Respiratory***- rhinitis, bronchospasm (dyspnoea, substernal tightness, wheezing), and laryngeal obstruction (stridor).

C. Management:

1. Management of airway:

- Oxygen is given by face mask. Endotracheal intubation may be required if patient cannot be ventilated adequately with face mask. In the presence of severe laryngeal oedema, cricothyroidotomy / tracheostomy may become necessary.

2. Adrenaline is the drug of choice:

- Adrenaline should be given while an attempt is made to obtain an IV access.
- A potent catecholamine with both alpha and beta adrenergic effects. The alpha activity augments arterial blood pressure by increasing peripheral vascular resistance. The beta effects relieve bronchospasm, augment cardiac activity, and inhibit mediator release.
- It is given in a dosage of 0.5-1mg (0.5-1ml of 1:1000) SC or IM and repeated twice at 20 min intervals if necessary.
- Patients with major airway compromise or hypotension should be given 5-10ml of 1:10,000 IV or via ETT. An infusion can also be started at a dose of 0.05-0.1mcg / kg / min to a maximum of 0.2mcg / kg / min (eg. 3mg in 50mls NS).

3. Glucagon:

- Glucagon is the agent of choice when adrenaline is relatively contraindicated eg. patients on beta blockers, patients with known coronary arterial disease, pregnant women, and patients with severe hypertension. It may be use as adjunct in patients who are refractory to adrenaline therapy.
- Glucagon enhances cAMP synthesis within the heart and GI tracts, leading to positive inotropy and chronotropy and smooth muscle relaxation.
- Glucagon can be given as SC or IM at a dose of 1mg. In severe anaphylaxis, IV 5-10 mg bolus followed by infusion 2-8mg / hr can be given.

4. **Volume expansion** with 500-1000ml of crystalloid or colloid, followed by titration to elicit acceptable blood pressure and urine output. Persistent hypotension despite initial pharmacological agents and fluid replacement is an indication for the use of inotropes.

5. **Inotropes:**

- Dopamine, isoprenaline and adrenaline infusions may be needed for patients with hypotension that does not respond to bolus adrenaline injections and IV fluids.

6. **Nebulized or inhaled ß-Agonists** as in asthma should be used to treat resistant bronchospasm.

7. **Aminophylline** may provide useful additional bronchodilatation in patients with refractory bronchospasm.

8. **Glucocorticoids** can be used to prevent recurrence or relapse of severe reactions. IV hydrocortisone 200mg 6 hourly. However, the use of these agents will have no immediate effect since they have an onset of action of 4-6 hours.

9. **Antihistamines:** Chlorpheniramine 10mg IV or diphenhydramine 25-50mg may be useful. Can be repeated 4-6hrly. Addition of H2 antagonists eg cimetidine or ranitidine oral or IV has also shown to be useful for persistent or recurrent symptoms.

10. **Other measures and further management:**

- Patients with mild to moderate reactions (urticaria or very mild bronchospasm) should be observed for a minimum of 6 hours.
- Patients with moderate to severe reactions (especially with orally ingested antigens) may relapse and should be admitted to the hospital.
- Ideally patients with severe anaphylaxis should be managed in ICU. Continuous ECG monitoring, close monitoring of ABG, CVP and blood pressure should be done.
- A regimen of 48-72 hours of antihistamines with or without H2 antigonist are usually given to prevent relapse.
- A short course of steroids (7-10 days) may be useful for patients who experience difficult bronchospasm , hypotension, or persistent bronchospasm.
- Inhaled beta2 agonist can be given for 48-72 hours.

_ SEPSIS AND SEPTIC SHOCK

- **Definition**: ***Sepsis*** is the systemic response to infection with two or more of the following: temperature greater than 38^{o}C or less than 36^{o}C, tachycardia, tachypnoea, WBC count over 12,000 / mm3 or under 4,000 / mm3, or greater than 10% band forms. Severe sepsis occurs with organ dysfunction, hypoperfusion (eg. lactic acidosis, oliguria, altered mental status) or hypotension (systolic BP < 90 mmHg or a reduction of 40 mmHg from baseline). ***Septic shock*** is sepsis-induced hypotension despite adequate fluid resuscitation along with organ perfusion abnormalities.
- The commonest pathogens are Escherichia coli, Staphylococcus aureus and epidermidis, and Streptococus pneumoniae (pneumococcus).

A. Clinical features

1. Early sepsis:

- Tachycardia (HR>100bpm) , tachypnoea (RR >20 pm), and fever. Hypothermia is often present in the elderly and those with chronic underlying diseases eg alcoholism , uraemia, or immunosuppression.
- Shaking chills (signify bacteraemia), confusion or other mental changes are often apparent in this early state.
- The skin remains warm in these patients despite hypotension.

2. Late sepsis:

- The skin now becomes cold and clammy with increasing tachycardia, pallor, and cyanosis.

- Oliguria and hypotension not responsive to fluids or pressor follow.

If a patient has unexplained hypotension, oliguria or confusional state associated with fever or reduced body temperature (<36^{O}C), a working diagnosis of sepsis syndrome should be made.

B. Urgent Investigations of the patient with sepsis and septic shock

- ***Full blood count*** (the white cell count may be low in overwhelming bacterial sepsis; low platelet count may reflect DIVC).
- ***Clotting screen*** if purpura, prolonged oozing from puncture sites, bleeding from surgical wounds or low platelet count.
- BUSE.
- ***Glucose*** (hypoglycaemia can complicate sepsis, especially in patients with liver disease).
- ***Amylase*** (if abdominal pain / tenderness).
- ***Chest X-ray.***
- ***ABG.***
- ***Blood cultures*** (2 sets). If suspected IV-line-related sepsis (CVP line, pulmonary artery catheter, indwelling IV catheter), take blood for culture via the lines and a further sample from a peripheral vain, change the central venous line or pulmonary artery catheter and send the tip for culture.
- ***Urine microscopy and culture.***
- ***Liver function.***
- ***Ultrasound of abdomen*** if abdominal source is suspected.
- ***Cerebrospinal fluid examination*** if suspected meningitis.
- ***Joint aspiration*** if suspected septic arthritis.
- ***Blood film for malaria*** in malaria endemic area.
- ***Widal test*** in typhoid endemic area.
- ***ECG*** if >60 or known cardiac disease.

C. Treatment

Strategy: The supportive management is extremely important, and must be performed meticulously well. It will keep the patient alive long enough for the antibiotics to take effect.

1. Supportive care and monitoring:
- Address ***ABCs*** of resuscitation.
- Hypoxaemia is common. ***Oxygen*** should be given.
- Where respiratory failure is severe, ***endotracheal intubation and mechanical ventilatory*** support is necessary.
- ***A central venous and arterial line*** and a ***CBD*** should be inserted.
- Heart rate, BP, rhythm, CVP and urine output are continuously monitored.

- A urine output over 0.5-0.7ml/kg per hour should be maintained. If severe oliguria persists in a well hydrated patient, IV ***mannitol*** 0.3/kg and/or IV ***frusemide*** 250-500mg can be given. These agents may increase renal blood flow and promote diuresis.
- Remove source of infection (eg. remove indwelling catheters or drainage of abscess).
- ***Central venous pressures (CVP)*** should be used to guide fluid resuscitation in the patient with septic shock (goal CVP = 8mmHg). Swan-Ganz catheter provides a better index of left ventricular function and should be placed in whom there is uncertainty about the role of cardiac function in the genesis of shock or in myocardial infarction with shock, to optimize fluid and inotrope management. The goal PCWP should be 10-15 mmHg.

2. Fluid replacement:

- The first line of treatment for hypotension in the patient with severe sepsis is isotonic IV fluids (either Ringer's lactate or normal saline).
- An initial fluid challenge of 1000ml is generally safe with close monitoring. Often 4-6 litres may be required.
- If there are any signs of pulmonary compromise (increasing dyspnoea, tachypnoea, tachycardia or decreasing SaO2) during this bolus, it should be stopped and pressor therapy instituted.
- The decision to use pressors generally comes after at least 1000-1500ml of crystalloid has been infused in an average-sized adult.

3. Inotropic agents:

- The goal of inotrope therapy is to maintain perfusion as indicated by mental status, urinary output, and skin perfusion at the lowest possible dose. Generally a systolic blood pressure above 90-110mmHg is necessary to maintain adequate tissue perfusion.

a. ***Dopamine*** generally is used as the first-line inotropic agent. Starting dose in septic shock not responsive to fluids is 5-10ug/kg/min. Above 20ug/kg/min, another pressor should be added.

b. ***Adrenaline or noradrenaline*** is a reasonable choice for a second-line agents. Adrenaline infusion can be started at a dose of 0.05-0.1ug/kg/min to a maximum of 0.2ug/kg/min (eg. 3mg in 50mls NS).

c. ***Dobutamine*** should be reserved for late sepsis. Initial dose is 2-10ug/kg/min, with a maximum dose of 30ug/kg/min.

4. Antibiotics:

- Timely use of an appropriate antibiotic regimen has been shown to improve survival and decrease the frequency of shock.
- Antibiotic choice should be guided by the presumed site of infection, as well as by the age and immune status of the patient (see table below).
- When possible, cultures should be taken prior to antibiotic treatment; however, patients in extremis should not have antibiotics withheld while awaiting for diagnostic testing.

- Typically 2-3 drug coverage (directed against both gram positive and gram negative) is recommended for sepsis.
- Empirical antibiotic recommendations for sepsis:

Source unknown

Community acquired	Enterobacteriaceae, S aureus, streptococcus	Third-generation cephalosporin and aminoglycoside +/- cloxacillin
IVDU (endocarditis)	S aureus, gram-negative, enterococci	Cloxacillin or vancomycin and aminoglycoside
Immunocompromised, neutropenic	Gram negative including P. aeruginosa, S aureus, Streptococcus epidermidis	Ceftazidime +/- aminoglycoside +/- vancomycin or cloxacillin *or* Piperacillin and aminoglycoside +/- vancomycin or cloxacillin *or* Imipenam +/- vancomycin or cloxacillin
With petechial rash	Meningococcus, gram-negative sepsis/DIC	Third-generation cephalosporin (ceftazidime if Pseudomonas suspected) and aminoglycoside

Source known

Meningitis	Refer to section on meningitis	
Pneumonia	Refer to section on pneumonia	
Endocarditis	Refer to section on endocarditis	
Abdominal/pelvic	Enterobacteriaceae, anaerobes, enterococci	Ampicillin/sulbactam or amoxycillin/clavulanic acid and aminoglycoside *or* Third-generation cephalosporin and metronidazole +/- aminoglycoside
Urinary	Enterobacteriaceae	Ampicillin/sulbactam or amoxycillin/clavulanic acid and aminoglycoside, *or* Third-generation cephalosporin and aminoglycoside (if gram -ve)
IV-line-related	S aureus, gram negative	Cloxacillin and aminoglycoside

5. New therapeutic approaches:

- Steroids have not been shown to be beneficial in sepsis, and they may increase mortality due to secondary infection.
- Monoclonal antibodies, tumour necrosis factor and interleukin-1 (IL-1) receptor antagonists have shown promise in limited studies and further trials are ongoing.

_ MALARIA

- Malaria is still a major health threat for those living in, visiting or returning from malaria-endemic areas.
- Four species of the protozoa Plasmodium infect humans: P. vivax, P. malariae and P. falciparum are endemic in Malaysia. P. ovale is not.
- The organism is transmitted by the bite of a female anopheline mosquito.
- The incubation period ranges from one to several weeks. Partial chemoprophylaxis or incomplete immunity can markedly prolong the incubation period to months or even years.
- 'Non-immune' individuals, who have not been exposed over time to the bites of Plasmodium-infected mosquitoes are more symptomatic at lower levels of parasitaemia than immune indivuals, who may have significant parasite loads without developing any associated symptoms.
- Infections with P. vivax, P. malariae and P. ovale are seldom fatal, but a delay in initiating proper treatment for mild P. falciparum infection can result in rapid progression to life-threathening illness.

A. Clinical features

_ Uncomplicated Malaria (all species):

- Fever.
- Chills.
- Headache.
- Malaise.
- Myalgia.
- The malarial paroxysm -rigor and fever followed by profuse diaphoresis and exhaustion - occurs at regular intervals are seldom seen.

_ Features of severe falciparum malaria:

1. ***CNS***
   Cerebral malaria
2. ***Renal***
   Haemoglobinuria (blackwater fever)
   Oliguria
   Uraemia (acute tubular necrosis)
3. ***Blood***
   Severe anaemia
   DIVC
4. ***Respiratory***
   Acute respiratory distress syndrome
5. ***Metabolic***
   Hypoglycaemia
   Metabolic acidosis
6. ***Gastrointestinal/liver***
   Diarrhoea
   Jaundice
   Splenic rupture
7. ***Other***
   Shock-hypotensive
   Hyperpyrexia
   Adrenal insufficiency-like syndrome

B. Investigations

- The definitive diagnosis is established by visualization of the parasite on Giemsa-stained thin and thick smears. In early infection, especially P. falciparum in which parasitized red cells are often sequestered from the bloodstream, parasitemia may be undetectable initially.
- When malaria is suspected but parasites are not visualized, repeated smears should be taken at least twice daily for 3 days to fully exclude malaria.
- FBC, ESR, BUSE, LFT, glucose, ABG, Se creatinine, UFEME, and CXR should also be done for complicated malaria.
- G6PD should be screened before the use of primaquine.
- Blood culture should be done in hypotensive patients or when superimposed gram negative sepsis is suspected.

C Management

* ***In Sarawak, a map delineating areas where chloroquine resistant P. falciparum is endemic is available and should be referred to before commencing treatment.***

I. Treatment of Falciparum malaria

1. When chloroquine resistance is suspected

- Quinine salt 600mg every 8 hourly for 7 days (10mg/kg 8hrly) plus (if quinine resistance known or suspected) Fansidar (pyrimethamine 25mg, sulfadoxine 500mg) 3 tablets as a single dose or (if Fansidar resistant) tetracycline 250mg 6hourly/Doxycycline 100mg/day for 7 days when renal function returns to normal

or

- Mefloquine base 20mg/kg as a single dose (max 1.5 g) or preferably as 2 divided doses 6-8 hours apart

or

- Halofantrine hydrochloride 500mg 8hourly for 3 doses and repeat after 1 week

2. When chloroquine resistance is not suspected

- Chloroquine base 600mg initially, then 300mg after 6-8 hours then 300mg daily for 2 days

Plus

Primaquine 15 mg daily for 3 days

@ **Alternative regime**

- Chloroquine 4 tabs (600mg base or 10mg base/kg), and primaquine 2 tabs (15mg) for 1st day

followed by

Chloroquine 3 tabs and primaquine 2 tabs orally for 2nd and 3rd days.

** Do not use chloroquine if it has been used for prophylaxis.*
** If the patient has not shown a clinical response to chloroquine (48-72 hrs for mild infections, 24 hrs for severe ones), parasitic resistance to chloroquine should be considered. Chloroquine should be stopped & treatment for chloroquine resistance P. falciparum started.*

3. In seriously ill patient (cerebral malaria, multiple complications), failure to retain ingested drugs or hyperparasitaemia (see definition)

- Loading dose of quinine salt 20mg/kg (max 1.4g) in 250 cc D5% over 4hours then after 12 hours maintenance dose of 10mg/kg (max 700mg) over 4 hours every 12 hours (until patient can swallow tablets to complete

the 7 days course) either followed by fansidar or tetracycline as above. If patient is still unable to swallow after 48 hrs or renal / liver impairment, continue IV quinine but reduce dosage by half (5-7mg / kg of quinine salt).

* ***Note:***

- Quinine salt is valid for quinine hydrochloride, dihydrochloride, and sulphate, not valid for quinine bisulphate.
- The loading dose of 20mg / kg should not be used if the patient has received quinine or quinidine or mefloquine or possibly halofantrine during the previous 24 hours.
- Quinine can cause hypotension if given too quickly. It can also cause hypoglycaemia. Therefore, when using IV quinine, BP & ECG monitoring should be done continuously to detect hypotension or arrhythmias.
- Adequate doses of quinine inevitably cause tinnitus; this is reversible and is not a reason to stop treatment.
- In addition to specific antimalarial chemotherapy, any complication of the disease must be treated eg. renal failure, ARDS, severe anaemia and shock (see below).
- If quinine hydrochloride is not available, quinidine gluconate can be used. A loading dose of 10mg / kg (salt) is given IV in 5% glucose 250cc over 1-2 hrs, followed by 0.02mg / kg / min (salt) until oral quinine can be given.

@ **<u>Alternative regime</u>**

- Quinine hydrochloride 600mg in 250cc 5% dextrose given over 4 hours ; 3 doses 8hrly on Day 1, 2 doses 12 hrly on Day 2 and a single dose on day 3.

  and

  Fansidar or tetracycline / doxycyline as mentioned above followed by oral quinine 10mg / kg 8 hrly to complete 7 days of treatment.

II. Treatment of complications in Falciparum Malaria

- Severe and complicated falciparum malaria is a medical emergency that requires ICU care and IV chemotherapy as rapidly as possible.
- Fluid, electrolyte, glucose & acid-base balance must be monitored. Intake & output should be carefully recorded. CVP measurement may also be needed.

1. Cerebral malaria:

- Malarial patients with signs of cerebral dysfunction eg. confusion, drowsiness, convulsions and abnormal behaviour should be regarded as cerebral malaria and treated as such.
- Convulsions should be controlled with diazepam. For recurrent seizures, IV phenytoin or phenobarbitone can be used.

- General and supportive care and specific chemotherapy with quinine as detailed earlier.
- It patients shows hypersensitivity to quinine, the quinine should be stopped and substituted with chloroquine 5mg / kg IV over 4 hours on a 12 hrly bases regimen for 2-3 days followed by tetracyline or doxycyline for 7 days.
- Dexamethasone, mannitol and heparin are contraindicated in cerebral malaria.

2. Severe Anaemia:
- Severe anaemia is defined as a haemotocrit of less 20% (Hb < 7g / dl).
- Packed cell should be transfused in severe anaemia. Monitor carefully to avoid fluid overload. Give small dose of frusemide (eg. IV 20mg). Where parasitaemia load is excessive, exchange transfusion may be considered and may be life saving.

3. Bleeding and clotting disturbance:
- This complication is due to DIVC.
- Appropriate treatment with FFP, platelet or fresh whole blood must be given.

4. Acute renal failure:
- Renal failure is defined as a urine output of less than 400 ml in 24 hrs and a raised serum creatinine failing to improve after rehydration.
- Catheterise the patient to obtain urine for analysis and monitor urine output. Rehydrate patient with N / saline till CVP is 5-10 cm H_20. If urine output remains poor after rehydration, IV frusemide or infusion can be given as in acute renal failure.
- Patients who are in established renal failure should be placed on a strict fluid balance. Monitor with daily / twice daily BUSE, se creatinine. Consider peritoneal dialysis if necessary.
- In patients with renal failure, the doses of quinine should be reduced to half. If possible, the drug levels should be checked and further dosages adjusted accordingly.

5. Pulmonary oedema:
- Give high concentration oxygen, prop patient upright.
- To give IV diuretic but most patient response poorly to diuretics. IV morphine or nitrates may be helpful in normotensive patient. The most effective way to reduce CVP is to venesect 250ml of blood from an adult. Blood transfusion may be needed later should anaemia be severe.
- Mechanical ventilation should be considered.

6. Hyperparasitaemia:
- Hyperparasitaemia is where the density of asexual forms P. falciparum in the peripheral blood exceeds 5% of erythrocytes or more than 250,000 parasites per ul at normal red cell count.
- The prognosis is worse in patients with hyperparasitaemia.

- Patients should be treated with IV chemotherapy and exchange transfusion has been used in a number of centers. This procedure, using 5-10 liters of donor blood, reduces parasitaemia dramatically.

7. Shock:

- Set up a CVP line and correct 'shock' with plasma expanders or normal saline. Consider inotrops eg. dopamine infusion if above measures fail.
- Persistent hypotension despite volume replacement should alert the clinician to the possibility of complicating septicaemia. Broad spectrum antibiotics should be started after taking blood cultures.
- If patient is on IV quinine or quinidine, consider drug induced cardiac depression.
- Hypoglycaemia should be corrected.

8. Intravascular haemolysis and haemoglobunuria:

- Management requires attention to renal function, fluid balance, and the possible need for blood transfusion.

9. Hypoglycaemia:

- Hypoglycaemia is defined as a blood glucose concentration of < 2.8 mmol/l (<50mg/dl).
- This condition may complicate severe malaria in any patient and may also develop in a patient receiving quinidine or quinine, as a result of hyperinsulinaemia induced by the drug.
- Correct hypoglycaemia with 50% dextrose. Use 5% dextrose rather than N/saline as infusion fluids. Check blood glucose 4-6 hourly in the first 48 hours.

10. Hyperthermia:

- Hyperthermia is defined as a rectal body temperature above $39^{o}C$.
- Hyperthermia should be treated by sponging with tepid water and fanning and with an antipyretic drug. Rectal paracetamol 0.5-1 g every 4 hours is a useful and safe regimen.

III. Treatment of Benign Malaria

- Chloroquine base 600mg initially, then 300mg after 6-8 hours then 300mg daily for 2 days
  Plus (in P. vivax and P. ovale)
  Primaquine 15 mg daily for 14-21 days (if G6PD normal)

IV. Treatment of Malaria in pregnancy

 # <u>Chloroquine sensitive falciparum and benign malaria</u>

- Chloroquine base 600mg initially, then 300mg after 6-8 hours then 300mg daily for 2 days

- Primaquine should be witheld in Vivax until after delivery as it is teratogenic. This can lead to relapses (retreat with chloroquine) and transmission but this is unavoidable. Chloroquine continued at a dose of 600mg each week during the pregnancy can also be used.

 # <u>Chloroquine resistant falciparum</u>

- The adult treatment doses of oral and IV quinine given above are safe in pregnant women. Halofantrine is contra-indicated in pregnancy and tetracycline should be avoided. Fansidar and mefloquine are also best avoided.

V. Treatment of patient with G6PD deficiency

- Chloroquine and quinine can be given as usual.
- Primaquine can be given as 30-45 mg once a week for 8 weeks.

VI. Monitoring

- For all malaria infections, blood smear should be repeated at daily (twice daily in severe infection). Within 48-72 hrs after start of treatment, patients usually become afebrile and improve clinically; with 48 hrs, parasitaemia is generally reduced by about 75% (initial increase may be noted during the first 6-12 hrs).

10. REFERENCE INTERVALS

1. Urea, electrolytes, liver function test: & miscellaneous tests:

Test	SI units	Conversion factor ∅/♦	Conventional units
Alanine amino-transferase (ALT)			5-40 IU/l
Albumin	35-55 g/l	0.1/10	3.5-5.5 g/dl
Alkaline phosphatase			30-130 IU/l
Aspartate amino-transferase (AST)			5-30 IU/l
Bicarbonate	22-28 mmol/l	1/1	22-28 meq/l
Bilirubin, total indirect direct	 5-17 umol/l 3.4-12 umol/l 1.7-5.0 umol/l	 0.0585/17.1	 0.3-1.0 mg/dl 0.2-0.7 mg/dl 0.1-0.3 mg/dl
C-reactive protein	0-10 mg/l		
Calcium	2.1-2.65 mmol/l	4/0.25	8.5-10.6 mg/dl
Chloride	95-105 mmol/l	1/1	95-105 meq/l
Cholesterol desirable, borderline high High	 <5.17 mmol/l 5.17-6.18mmol/l >6.18 mmol/l	 38.7/0.0259	 <200 mg/dl 200-239 mg/dl >239 mg/dl
Creatinine	60-130 umol/l	0.0113/88.4	0.6-1.5 mg/dl
Creatinine kinase			0-170 IU/l
Gamma Glutamyltransferase (GGT)			0-30 IU/l
Globulin	20-35 g/l	0.1/10	2.0-3.5 g/dl
Glucose (fasting)	3.5-6 mmol/l	18/0.055	63-110 mg/dl
Lactate	0.6-1.8 mmol/l	1/1	0.6-1.8 meq/l
Magnesium	0.7-1 mmol/l	2/0.5	1.4-2 meq/l
Osmolality, plasma			280-295 mosmol/kg
PaCO2	4.7-6 kPa	7.5/0.1333	35-45 mm Hg
PaO2	10.7-13.3 kPa	7.5/0.1333	80-100 mm Hg
PH	7.35-7.45		
Phosphate	0.8-1.5 mmol/l	3.1/0.323	2.5-4.65 mg/dl
Potassium	3.5-5 mmol/l	1/1	3.5-5 meq/l
Sodium	135-145 mmol/l	1/1	135-145 meq/l
Total protein	65-80 g/l	0.1/10	6.5-8.0 g/dl
Triglyceride (fasting)	<2.8 mmol/l	88.5/0.0113	<250 mg/dl
Urea	2.5-6.5 mmol/l	6.01/0.166	15-40 mg/dl
Uric acid	180-420 umol/l	0.0168/59.5	3.0-7.0 mg/dl

2. Haematology:

Test	SI units	Conversion factor ∅/♦	Conventional units
Hb Males Females			 14-18 g / dl 12-16 g / dl
MCH	27-32 pg / cell		
MCHC	320-360 g / l		32-36 g / dl
MCV	76-98 fl		
Reticulocyte count			0.2-2%
Platelet count	150-400 x 10^9 / l	1 / 1	150-400 x 1000 / ul
White blood count	4-11 x 10^9 / l	1 / 1	4-11 x 1000 / ul
Differential counts Neutrophils Lymphocytes Eosinophils Basophils Monocytes	 2-7.5 x 10^9 / l 1.5-4 x 10^9 / l 0.04-0.4x 10^9 / l 0-0.1 x 10^9 / l 0.2-0.8 x 10^9 / l		 40-75% 20-45% 1-6% 0-1% 2-10%
ESR	0-20 mm in the first hour		
Prothrombin time	11-13 sec		
Activated PTT	20-35 sec		
Thrombin time	15-20 sec		
Bleeding time	2-9.5 mins		
Fibrinogen	2-4 umol / l	100 / 0.01	200-400 mg / dl

3. Hormone levels:

Test	SI units	Conversion factor ∅/♦	Conventional units
Thyroxine, total (T4) free	 60-160 nmol / l 10.3-34.8 pmol / l	 0.0777 / 12.87	 4.7-12 ug / dl 0.8-2.7ng / dl
T3	65-195 ng / dl	0.01536 / 65.1	1-3 nmol / l
TSH	0.5-5 mU / l		0.5-5 uU / ml

11. INDEX